EARLY IMPLEMENTATION OF GUIDELINES FOR MANAGING YOUNG INFANTS WITH INFECTION IN RURAL BANGLADESH: AN IMPLEMENTATION RESEARCH STUDY

by
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Abstract

Background: Neonatal infections remain a leading cause of newborn deaths globally. In 2015, the World Health Organization (WHO) issued guidelines for managing possible serious bacterial infection (PSBI) in young infants (0-59 days) using simplified antibiotic regimens when compliance with hospital referral is not feasible. Bangladesh was one of the first countries to adopt WHO's guidelines for implementation. This implementation research study assessed fidelity and acceptability of the guidelines in three rural sub-districts of Bangladesh during August 2015-August 2016.

Methods: This study was conducted in 19 primary health centers and their catchment areas. Facility readiness was assessed using checklists completed by study staff at three time points and case management data were extracted from registers weekly. Questionnaires were administered to caregivers of cases to assess treatment adherence. To measure fidelity, we assessed 1) trends in provider adherence to guidelines; and 2) conducted a multinomial logistic regression to assess patterns and determinants of caregiver adherence to the oral amoxicillin regimen. Caregiver acceptability was measured for key guideline components including acceptance of referral and simplified antibiotic treatment. Focus group discussions and in-depth interviews with providers and caregivers were conducted to identify barriers and facilitators for implementation fidelity and acceptability.

Results: Provider errors in classification and antibiotic treatment were highest at the beginning of the study period, but performance improved over time. Qualitative data suggest errors in early implementation may be due to providers learning new methods for assessment and treatment, and some providers' concerns about the efficacy of simplified antibiotic regimens. Few caregivers accepted referral to the hospital, which was attributed to previous negative experiences at these facilities. Caregivers that received follow-up from the provider during the illness episode were less likely to provide fewer than the recommended doses of oral amoxicillin. Acceptability of

simplified antibiotic treatment was high, especially when caregivers had trust and good communication with the provider.

Conclusions: Clinical supervision and mentoring are important drivers of implementation when introducing complex guidelines. Strategies to monitor early performance and targeted supports are important for enhancing implementation fidelity. Counseling on continued treatment and follow-up by the provider improved caregiver acceptability and adherence to the simplified antibiotic regimen.

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Abbreviations & Key Definitions

CHW: Community Health Worker

CI: Critical illness (CI) in a young infant (0-59 days) is characterized by the presence of any of the following signs: unconscious, convulsions or history of convulsions, unable to feed at all, no movement on stimulation, unable to cry, persistent vomiting, bulging fontanelle, cyanosis.

CSI: Clinical severe infection (CSI) in a young infant (0–59 days old) is characterized by the presence of at least one of the following signs: severe chest in-drawing, hypothermia (<35.5C), fever (>37.5C), movement only on stimulation, not feeding well (based on history and observation).

DGFP: Directorate General of Family Planning

DGHS: Directorate General of Health Services

FGD: Focus Group Discussion

FPI: Family Planning Inspector

FWV: Family Welfare Visitor

IFB (<7 D): Isolated Fast Breathing (IFB), characterized by a respiratory rate of greater than or equal to 60 breaths per minute as the only sign of infection, in an infant 0-6 days old.

IMCI: Integrated Management of Childhood Illness

MaMoni HSS: MaMoni Health System Strengthening project

MOHFW: Ministry of Health and Family Welfare

PSBI: Possible Serious Bacterial Infection (PSBI) is a clinical syndrome used in the Integrated Management of Childhood Illness package referring to a sick young infant (0-59 days old) who requires urgent referral to hospital. Per WHO guidelines, young infants with one or more clinical signs of possible infection:

- Respiratory rate >=60 per minute if <7 days
- Severe chest in-drawing
- Hypothermia (<35.5 ºC)
- Fever (>=38.0 ºC)
- No movement or movement only upon stimulation
- Convulsions
- Feeding poorly or not feeding at all

SACMO: Sub-Assistant Community Medical Officers

SAT: Simplified Antibiotic Therapy

UH&FWC: Union Health & Family Welfare Centers

UHC: Upazila Health Complex

WHO: World Health Organization

Chapter 1. Introduction

Bangladesh observed an impressive decline in under-five mortality and achieved the fourth Millennium Development Goal for child survival (1). Deaths in neonates, however, have been declining at a lower rate than mortality in older children. As a result, the proportion of under-five deaths occurring in the neonatal period increased from 44% in 1990 to 62% in 2015 (1). With a neonatal mortality rate of 28 per 1,000 livebirths, the country experiences over 74,000 neonatal deaths annually. Most of these deaths are due to three causes: prematurity, infections, and intrapartum-related complications (1-3). Progress towards reducing neonatal mortality due to these three causes is imperative for Bangladesh to achieve the Sustainable Development Goals target of 12 neonatal deaths per 1,000 livebirths by 2030 (1).

Neonatal infections, including sepsis, meningitis and pneumonia, remain a leading cause of newborn death in Bangladesh. Severe infections have a rapid onset and definitive diagnosis is often not possible (4). A recent population-based cohort study in rural Bangladesh attributed 46% of all neonatal deaths to serious infections (5). The World Health Organization (WHO) recommends that young infants (0-59 days) with signs of possible serious bacterial infection (PSBI) be referred to hospitals and treated with a seven to 10-day course of a combination of two injectable antibiotics: gentamicin and either penicillin or ampicillin (6). However, in resource-limited settings, many young infants with PSBI do not receive the recommended inpatient treatment because hospital care may not be accessible, acceptable or affordable (6). Based on trial data from South Asia and sub-Saharan Africa, WHO issued new guidelines in 2015 for managing PSBI in young infants, when referral is not feasible for families, with simpler antibiotic regimens that include fewer doses of injectable antibiotics coupled with oral antibiotics delivered by care providers closer to the community (6-9). Findings from these studies also contributed to a new evidence-base of implementation strategies for safely delivering outpatient treatment to newborns in resource-constrained settings (4, 9-13).

Recognizing the need to increase access to and coverage of newborn health services, particularly management of PSBI, the Government of Bangladesh developed and implemented the National Newborn Health Program as part of the 4th Health, Population and Nutrition Sector Program (14). Bangladesh was one of the first countries to adopt the WHO guidelines and adapt them into national guidelines as part of a Comprehensive Newborn Care Package of interventions targeting leading causes of neonatal death in the country (14-16). Effective implementation of the updated guidelines requires multi-stakeholder partnership and collaboration across the health system (17). Implementation research provides an opportunity to study how interventions work in real world conditions, aiming to bridge the gap between evidence and practice to accelerate development and equitable delivery of health services (4, 17, 18).

Guided by principles of implementation research, Johns Hopkins University and other development partners collaborated with Bangladesh's Ministry of Health and Family Welfare (MOHFW) to support the rollout of national guidelines for managing infections in young infants at outpatient primary health centers in selected districts (16). The aim of this implementation research study is to share early program learnings and provide recommendations for strengthening the program as it is scaled-up in Bangladesh. This dissertation will discuss support to the MOHFW-led implementation of the guidelines in 3 sub-districts of 2 districts in Bangladesh, focusing on implementation strategies—informed by WHO's guidance and embedded in the local context (12, 13)— and assessment of the implementation research outcomes of fidelity and acceptability of the guidelines (Figure 1).

The first chapter of this dissertation provides background on the development of WHO's guidelines for managing PSBI in young infants when hospital referral is not feasible, the Government of Bangladesh's adoption of WHO's guidance and adaption into national guidelines, and rationale for studying implementation of the guidelines (Figure 1). Chapter two focuses on the study context and intervention and provides an overview of the parent study's implementation

support and embedded mixed methods evaluation activities. Chapters 3-5 discuss the main findings of this dissertation by study objective:

1) Provider performance and facility readiness for managing infections in young infants in primary care facilities (Chapter 3)
2) Caregiver acceptability of the guidelines for managing young infants with possible serious bacterial infections (PSBI) in primary care facilities (Chapter 4)
3) Patterns and determinants of caregiver non-adherence to oral amoxicillin for sick young infants receiving simplified antibiotic treatment (Chapter 5)

Finally, Chapter 6 provides a summary of the study's findings, including implications for programs and policies, study strengths and limitations, and opportunities for future research.

1.1 Background

Global guidance—Development of guidelines for management of PSBI in young infants when hospital referral is not feasible

In 1999, findings from a field trial in Gadchiroli, India, demonstrated that home-based care of newborns, including management of sepsis, could cut neonatal mortality in half (19). Subsequent trials also achieved substantial reductions in neonatal mortality through implementation of a package of community-based health care interventions (19-21). In rural Bangladesh, a package of newborn health interventions delivered through antenatal and early postnatal home visits contributed to a 34% reduction in neonatal mortality (20, 22). A commonality across these studies was an intervention package, which included home visits during the neonatal period, identification and treatment of sick infants by community health workers and facilitation of referral to hospitals when accepted by the families (19, 21-23).

In 2007, a research initiative organized through the collaborative efforts of WHO, USAID, and Save the Children/Saving Newborn Live (SC/SNL) convened multiple stakeholders to review the existing evidence on neonatal and young infant care. The goal was to identify simple, safe and effective treatment regimens that could be provided to young infants with

suspected infections when inpatient care was not feasible for families (24). The panel concluded that the current evidence was insufficient to recommend antibiotic treatment of severe infections at the community-level. Experts called for additional research on shorter-course antibiotic therapies, simple diagnostic algorithms, and optimal delivery strategies appropriate for severely resource-constrained health systems (24).

In response to this call for additional research, three randomized, open-label, equivalency trials evaluated simplified antibiotic regimens—including fewer injections combined with oral amoxicillin—for managing PSBI in young infants in community settings when compliance with hospital referral was not feasible for families. These trials were conducted in Bangladesh, Pakistan and three countries in Africa— Democratic Republic of the Congo (DRC), Kenya and Nigeria. Study protocols were harmonized, but models for service delivery varied based on the context to allow integration into existing programs and test delivery strategies in different resource-constrained settings (25). Investigators concluded that simplified antibiotic regimens were as efficacious as the standard regimen—procaine benzylpenicillin and gentamicin once per day for seven days—in treating clinical severe infection in young infants when the families refused hospital admission (7, 9, 26). The Africa trials also assessed a simplified treatment option, which included no injections, for young infants presenting with fast breathing as the only sign of PSBI. They found that oral amoxicillin twice per day for seven days was as efficacious as the standard injectable regimen for treating isolated fast breathing in these infants (9).

Based on a systematic review of the evidence available from these trials, in 2015, the WHO issued new guidelines for resource-limited settings for outpatient management of PSBI in young infants when the family does not accept or cannot access hospital care (6, 7, 9, 26). The WHO recommends if inpatient care is not feasible for families, the sick infant should be managed in outpatient settings by trained providers according to one of two treatment regimens (6, 12, 13):

- **Option 1**: Intramuscular gentamicin (5–7.5 mg/kg [for low-birth-weight infants gentamicin 3–4 mg/kg]) once daily for seven days and twice daily oral amoxicillin (50 mg/kg per dose) for seven days
- **Option 2**: Intramuscular gentamicin (5–7.5 mg/kg [for low-birth-weight infants gentamicin 3–4 mg/kg]) once daily for two days and twice daily oral amoxicillin (50 mg/kg per dose) for seven days. Close follow-up is essential. A careful assessment on day 4 is mandatory.

It is expected that individual countries will adapt the WHO recommendations based on their local social, economic and cultural contexts (6). For example, national governments are expected to select Option 1 or Option 2 based on the expected feasibility of providing seven versus two days of injectable antibiotics in their public sector outpatient facilities (6, 12, 13).

National policy development—Bangladesh's adoption of WHO's guidelines and adaption into national guidelines

Since the launch of Bangladesh's National Neonatal Health Strategy in 2009, newborn health policies have been developed through a series of consultations with newborn health experts, development partners, and global stakeholders under the leadership of the National Technical Working Committee for Newborn Health (NTWC-NBH) (14, 27). In 2013, the Government of Bangladesh reinforced its commitment to ending preventable child deaths by 2035 through the *A Promise Renewed* declaration and identified the need for scale-up of evidence-based newborn health interventions to reduce neonatal mortality (15). The NTWC-NBH recommended four key newborn health interventions targeting the top causes of neonatal death in the country: prematurity, infections, and intrapartum-related complications (1, 2, 14). These interventions were approved by the National Core Committee on Neonatal Health, and NTWC-NBH guided the development of national guidelines for each of the four interventions—including prevention and timely treatment of neonatal infections—as part of a Comprehensive Newborn

Care Package (15, 16, 27). Bangladesh adopted the WHO recommendations and adapted them into national guidelines for inclusion in the Comprehensive Newborn Care Package (14, 16).

Guidance on implementation strategies and implementation research to support rollout of guidelines in resource-constrained settings

Findings from the globally coordinated studies on simplified antibiotic treatment also contributed to a new evidence-base of implementation strategies for safely delivering outpatient treatment in severely resource-constrained settings (4, 9-12) (Figure 1). In 2015, WHO spearheaded efforts to conduct implementation research studies across multiple country sites to prospectively study implementation outcomes and inform guidance on operationalizing the guidelines (12). Implementation research provides an opportunity to understand 'how' and 'why' evidence-informed interventions lead to health impact (17, 18). It involves working with multiple stakeholders including government managers, healthcare providers and the beneficiaries of services (18).

The WHO-coordinated implementation research studies included multiple demonstration sites in Bangladesh, Pakistan, India, Nigeria, Malawi, DRC, and Ethiopia (12). An USAID-funded implementation research study was undertaken in three different districts of Bangladesh to operationalize and evaluate adoption of the new guidelines in primary health facilities (4). Study protocols were harmonized across the study sites, but technical support varied based on the local context and health system. Mixed methods data collection was embedded in program rollout and lessons around implementation were shared across demonstration sites in periodic meetings with stakeholders (4, 6, 12).

Implementation research outcome variables evaluated in dissertation objectives

The study objectives of this dissertation focus on evaluation of the fidelity and acceptability of the intervention and relevant implementation strategies—shaded boxes in Figure 1. *Fidelity* is defined as the extent to which an intervention is implemented as intended in the

original protocol (28, 29). Evidence-based practice often assumes that an intervention is being implemented in accordance with the published recommendations, which may be problematic in real-world delivery systems (29, 30). It has been suggested that implementation fidelity acts as a potential moderator of the relationship between a public health intervention and the intended health outcomes (17, 29, 30). In other words, understanding and measuring intervention fidelity enables researchers and practitioners to better understand how and why an intervention works and the degree to which outcomes can be improved (30).

Implementation fidelity is described and defined in the literature by five dimensions: adherence, quality of delivery, program component differentiation (i.e., elements essential for program success), exposure to the intervention, and participant responsiveness (29, 30). For this study, implementation fidelity is assessed for provider adherence to the treatment guidelines and caregiver adherence to the oral amoxicillin regimen.

Acceptability is the perception among implementation stakeholders that an intervention is agreeable or satisfactory and is typically measured based on different aspects of the intervention and through the perspectives of various stakeholders (31). Acceptability is an important precursor to adoption of an intervention and will likely affect the long-term sustainability of the intervention (18, 31). In this study, we assessed caregiver acceptability of the guidelines from the perspective of both providers and caregivers.

Expected health outcomes and impact

The updated infection management guidelines aim to increase coverage of treatment for newborn infections through provision of public sector care that more affordable, accessible, and acceptable for families (6, 12, 32). The findings from this study will contribute to the global efforts to increase treatment access for families of young infants in low-resource settings that are unable to seek hospital care, which has the potential to reduce neonatal mortality globally due to serious infections.

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1.3 Figures for Introduction

Figure 1. Conceptual framework for implementation research study objectives evaluated in this dissertation

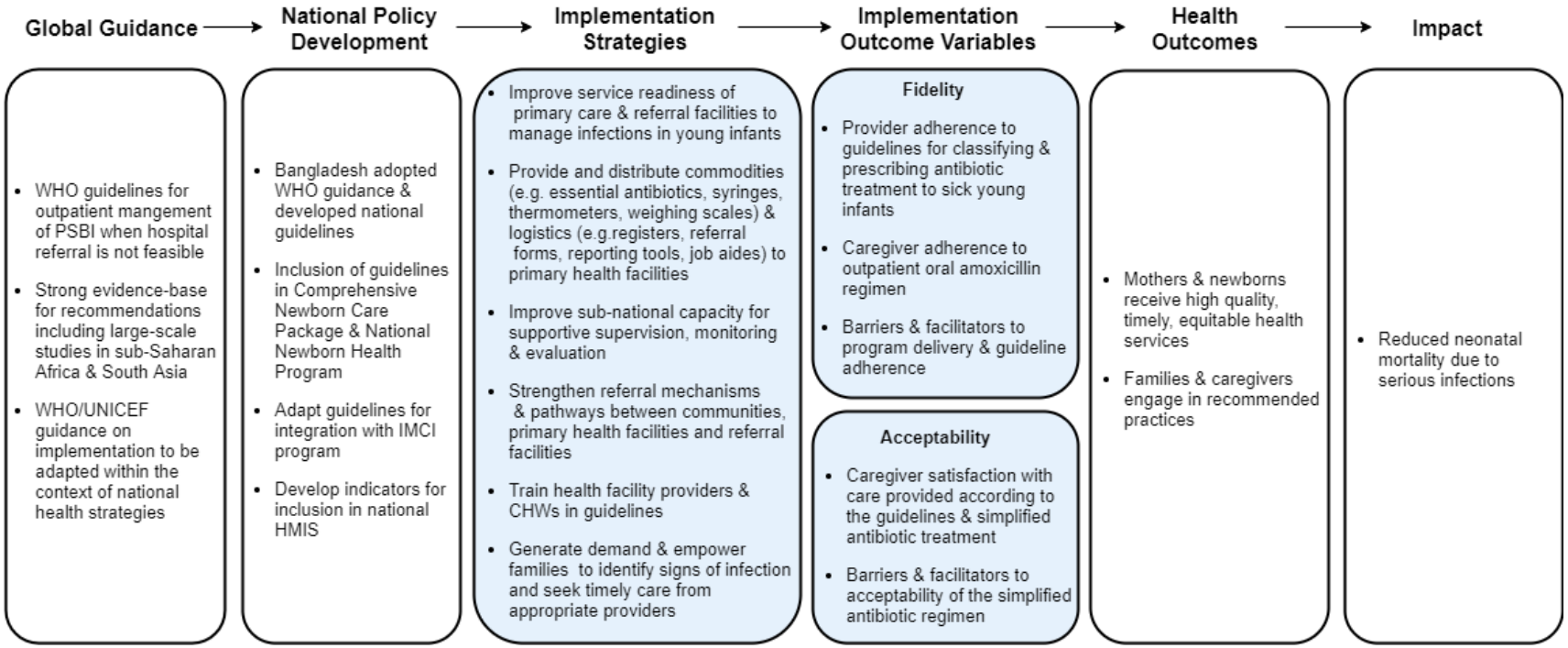

Figure legend: Implementation strategies recommended by WHO and adapted to local context (6, 12, 13). Shaded boxes include the implementation strategies supported by implementation partners and outcomes evaluated in this implementation research study.

Chapter 2. Methods

The three objectives of this dissertation are discussed in the subsequent chapters (Chapters 3-5). Each aim was nested in the USAID-funded, JHU-led parent study *Implementation research to support Bangladesh Ministry of Health and Family Welfare to implement its national guidelines for management of infections in young infants in two rural districts.* This chapter provides and overview of the parent study including the study context and intervention, implementation support activities and embedded mixed methods evaluation. The objective-specific implementation strategies, data collection methods, and analyses are discussed in the subsequent chapters to improve clarity for the objective-specific results and recommendations.

2.1 Context and intervention

Bangladesh is in the northeastern part of South Asia. Bangladesh is divided into eight administrative divisions, which are further divided into districts and sub-districts. In rural areas, sub-districts are divided into unions, then into wards (1). Our study area included union-level health centers in two sub-districts of Sylhet in Sylhet division and one sub-district in Lakshmipur in Chittagong division. Sylhet and Chittagong are historically low performing divisions of Bangladesh for maternal, newborn and child health indicators, including low rates of facility delivery and skilled attendants at birth (1). According to the 2014 DHS, Sylhet and Chittagong divisions had the highest fertility rates (2.9 and 2.5 respectively) and the highest proportion of unmet family planning need (18% and 17% respectively) in the country (1). Mothers in Sylhet are also the least likely to receive antenatal care from a medically trained provider. When compared with the rest of the country, these mothers also had the lowest proportion of births in facilities and lowest proportion of births attended by a skilled provider (27.1%) (1). In Chittagong, more mothers delivered in facilities (35.2%) and a higher proportion of births were attended by a medically trained provider (43.9%), but performance on these indicators still lags behind other divisions (1).

Health services in Bangladesh are provided through both public and private sectors and involve multiple actors. The country's pluralistic health system includes the MOHFW, the private sector (formal and informal), non-governmental organizations (NGOs), and there is significant influence from the international donor community (2, 3). These stakeholders are key actors in planning, financing and supporting service delivery of health programs (2). Bangladesh's MOHFW is responsible for policymaking, while implementation of those policies is the responsibility of different directorate generals. The Directorate General of Health Services (DGHS) and Directorate General of Family Planning (DGFP) are the two most important ones in terms of service delivery (2-4). The MOHFW maintains a three-tier system for delivering public health care services at all administrative levels and follows the IMCI protocol for management of sick children in primary health facilities (Figure 1) (1-3, 5, 6).

Targeted primary health facilities for implementation of Bangladesh's national guidelines are Union Health & Family Welfare Centers (UH&FWC [catchment ~25,000 persons]) (7). In the past, UH&FWCs have been largely under-utilized by communities and many were not fully functional due to staff shortages and insufficient equipment (2, 3, 8). These facilities provide outpatient services and are generally staffed by 2-3 formally trained providers—the Sub-Assistant Community Medical Officers (SACMO) and the Family Welfare Visitor (FWV). Some of these facilities have a position for a doctor available, but these posts are often vacant (2, 3, 9). The SACMO training and position is equivalent to a Clinical Officer in other contexts, such as sub-Saharan Africa. The SACMO has 3 years training on general healthcare, including child health, from a Government Medical Assistant Training School (3). The FWV has at least 18 months training from a private or government facility on midwifery and contraceptive management (2, 3, 5). In primary health care facilities, services are highly subsidized by the government, requiring no payments from patients (2, 4).

The SACMO is the designated provider for assessing, classifying and treating young infants according to the adapted WHO guidelines. To aid these workers in identifying sick

infants, the Bangladesh guidelines include a clinical algorithm for classifying signs of infection in young infants, guidance on antibiotic treatment, referral advice and follow-up (7). The algorithm is designed to have high sensitivity—as to not miss cases—and includes seven signs of PSBI (fever, hypothermia, convulsions, respiratory rate ≥60 breaths per minute if infant is <7 days, severe chest in-drawing, no movement or movement only upon stimulation, feeding poorly or not feeding at all) as well as other important signs of serious illness (7, 10, 11). If signs of infection are identified, then the SACMO classifies the infant as one of four sub-categories of infection—Critical Illness (CI), Clinical Severe Infection (CSI), Isolated Fast Breathing (IFB), or Local Bacterial Infection (LBI) (Figure 2). Accordingly, the SACMO provides the first dose of antibiotics based on the infant's weight and refers the infants with signs of PSBI (i.e., CI, CSI, and very young infants [0-6 days] with IFB) to the sub-district hospital (Upazila Health Complex [UHC]; catchment area ~250,000 persons) for inpatient care (5, 7). According to the new guidelines, young infants aged 7-59 days with fast breathing as the only sign of illness are no longer referred to the sub-district hospital. These infants receive outpatient treatment with oral amoxicillin—twice per day for seven days (5, 7).

Young infants classified as CSI or IFB (<7D) whose families decline hospital referral are eligible for simplified antibiotic treatment with injectable gentamicin once daily for two days and oral amoxicillin twice daily for seven days. Hospital referral is the only option for critically ill infants. Caregivers of infants with CSI that decline referral are instructed to return to the UH&FWC the next day for the 2nd gentamicin injection. Infants with IFB (<7D) only receive the oral amoxicillin regimen. The FWV may provide the 2nd injection if the SACMO is not present at the UH&FWC. The SACMO follows-up with caregivers over telephone on the fourth day, and if the infant's condition has not improved, advises the caregivers to seek care at the UHC. On the eighth day of treatment, the family receives a home visit from the Family Planning Inspector (FPI), who are trained as supervisors of frontline workers, to assess treatment compliance and the condition of the infant (7).

2.2 Overview of parent study

The parent study for this dissertation—*Implementation research to support Bangladesh Ministry of Health and Family Welfare to implement its national guidelines for management of infections in young infants in two rural districts*—was conducted as a part of partner support for early implementation of the PSBI guidelines in Bangladesh. Within the first year of implementation of the updated guidelines (August 2015-August 2016), the MOHFW received support from Projahnmo and the MaMoni Health Systems Strengthening (HSS) project in 3 sub-districts of the selected districts, Sylhet and Lakshmipur respectively. Projahnmo is a partnership of Johns Hopkins University with the Bangladesh MOHFW and other Bangladeshi institutions including International Centre for Diarrheal Disease Research, Bangladesh (icddr,b), Shimantik, and the Child Health Research Foundation (CHRF). Projahnmo has been working in Sylhet since 2001 and has experience with conducting surveillance through a team of trained community health workers and local managers (12). The USAID-funded MaMoni HSS project is implemented by the Maternal and Child Health Program (MCHIP) in six districts of Bangladesh with the goal of improving utilization of integrated maternal, newborn, child health, family planning and nutritional services (13). The project inputs were primarily focused on improving the performance and capacity of health services at the district-level. Since 2003, MaMoni HSS project has been working in all upazilas in Lakshmipur to strengthen district-level health systems and promote scale-up on maternal, neonatal and child health, family planning and nutrition interventions (13). For this study, MaMoni HSS provided support to the implementation of the infection management guidelines in one sub-district of Lakshmipur (Ramganj). Both Projahnmo and MaMoni HSS partnered with the MOHFW to ensure the implementation readiness of UH&FWCs to manage infections in young infants, including support to the training and supervision of providers in the infection management guidelines

Health centers in the project areas were selected for targeted support based on the presence of the designated provider (i.e., SACMO) at the facility. Nine health centers in Zakiganj and Kanaighat sub-districts of Sylhet and 10 health centers in Ramganj sub-district of Lakshmipur received implementation support and were included in the implementation research study. Project partners' implementation strategies focused on improving readiness of targeted health centers to implement the guidelines, supporting the MOHFW to build capacity of providers, and promoted awareness and community engagement with the public sector healthcare system. Additional details on our implementation strategies are provided in Supplemental Table 1.

The measurement and evaluation component of this study was led by JHU with support of MaMoni HSS in Lakshmipur and Projahnmo in Sylhet, utilizing a mixed methods approach to assess the following implementation research objectives:

1) Examine feasibility of implementation of the newly developed infection management guidelines in young infants at UH&FWCs through outpatient services when referral is not accepted
2) Assess the acceptability of infection management services delivered on an outpatient basis at UH&FWCs among the parents and families of young infants
3) Measure caregiver knowledge and coverage of infection management for young infants
4) Assess the compliance of the families to the referral advice and new treatment regimen for young infant infections delivered at UH&FWCs
5) Document the safety of the injectable antibiotic therapies delivered at union-level facilities as per national guidelines for infants classified as clinical severe infection who refuse referral advice
6) Identify the enabling and hindering factors, and develop strategies to address barriers to the implementation of the national guidelines for management of infections of young infants at the union-level health facilities

To assess these outcomes, mixed methods data collection activities were carried out in 19 unions located in Sylhet (N=9) and Lakshmipur (N=10). In the parent study, quantitative data collection included rolling household surveys, health facility checklists, extraction of case data from health provider registers for young infants, and treatment adherence questionnaires with caregivers of infection cases in the community. Qualitative data was collected through process documentation activities, in-depth interviews with senior level program implementers, and in-depth interviews and focus group discussions with healthcare providers and caregivers. Over the course of the one-year implementation research study, two stakeholder workshops were held in Dhaka. Through these workshops, implementation partners shared early learnings from implementation support and evaluation activities and worked together to develop solutions to better support subsequent implementation of the guidelines.

2.3 Protection of human subjects

The parent study was submitted and approved by the Johns Hopkins School of Public Health Institutional Review Board (JHSPH IRB) and the Ethical Review Committee of the Bangladesh Institute of Child Health (BICH) prior to study initiation. The JHSPH IRB granted a waiver for the health facility checklist as non-human subjects research. For the household survey and the follow-up with cases in the community, we developed written informed consents, in both English and Bengali, at an appropriate comprehension level for all respondents for each activity. The consent forms for all study activities were approved by JHSPH IRB as verbal consent forms. Thus, research assistants read aloud the informed consent document to respondents prior to beginning the survey, questionnaire or interview. Informed consent was obtained for each activity. As part of the informed consent procedure and document, the respondent was reassured that they may withdraw participation at any time without penalty or consequence to their infant's care. Data collectors were trained in research ethics and the informed consent process following

the JHSPH IRB guide for training field researchers. Each data collector was also given a copy of the translated version in Bangla.

The study activities were considered low risk to participants with the primary risk being to their privacy. Nevertheless, our research team took precautions to ensure the respondents' privacy and sensitive information was protected throughout the study period. Data collectors informed the participants that the study team would work to keep their identity—and the identity of their infant—confidential. As part of the study team's efforts to maintain confidentiality, all questionnaires and documents with identifiers were kept under lock and key and their names were not shared with people outside of the study. Additionally, we took precautions when sharing findings from the interviews with health providers to not disclose identifying information about their specific position or facility affiliation.

2.4 Dissertation study objectives nested in parent study

The subsequent chapters of this dissertation discuss mixed methods findings on implementation fidelity and acceptability of the guidelines from the perspectives of healthcare providers and caregivers (Table 1). Each paper will contribute to the larger study objectives through assessing health facility readiness and provider performance on the guidelines, caregiver acceptability of care provided according to the guidelines, and caregiver adherence to the home-based oral amoxicillin regimen.

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2.6 Tables for Chapter 2

Table 1. Framework of implementation research outcomes and measures by dissertation study objective

Implementation Research Study Objectives			Measures		Data Sources	
Outcome	**Definition**	**Research Questions**	**Quantitative Indicators**	**Qualitative Themes**	**Quantitative**	**Qualitative**
Paper 1: Provider performance and facility readiness for managing infections in young infants in primary care facilities						
Fidelity	The extent to which the intervention was implemented as intended in the original protocol	Were health systems supports available to ensure providers could deliver the program as planned?	Change in proportion of facilities with essential commodities and frequency of supervision throughout the study period	Providers' perceptions of barriers and facilitators to program implementation	Health facility checklist Provider registers	Provider interviews and group discussions
		To what extent did providers adhere to the guidelines?	Change in provider performance on the guidelines over the study period			
Paper 2: Caregiver acceptability of the guidelines for managing young infants with possible serious bacterial infections (PSBI) in primary care facilities						
Acceptability	Perception among stakeholders that the intervention is	Where were there gaps in service delivery and care of PSBI cases?	Proportion of caregivers that accepted referral, returned to the facility and received follow-up from the provider	Providers' and caregivers' perceptions of the barriers and facilitators to	Provider registers	Provider interviews and group discussions

Implementation Research Study Objectives			Measures		Data Sources	
Outcome	**Definition**	**Research Questions**	**Quantitative Indicators**	**Qualitative Themes**	**Quantitative**	**Qualitative**
	agreeable or satisfactory	What was the uptake of the intervention by families in the community?	Percent of expected PSBI cases that sought care at study area health centers	acceptability of the guidelines		Caregiver interviews and group discussions
Paper 3: Patterns and determinants of caregiver non-adherence to oral amoxicillin for sick young infants receiving simplified antibiotic treatment in rural Bangladesh						
Fidelity	The extent to which the intervention was implemented as intended in the original protocol	To what extent did caregivers adhere to the oral amoxicillin regimen?	Proportion of caregivers that adhered to the recommended number of doses	Caregivers' perceptions of barriers and facilitators to providing oral amoxicillin treatment at home	Provider registers Treatment adherence questionnaire	Caregiver interviews and group discussions
		What are the determinants of non-adherence?	Relative risk of non-adherence given relevant predictor variables			

Supplemental Table 1. Project partners support to MOHFW to strengthen implementation readiness and operationalize the infection management guidelines

Component of Implementation Readiness	Challenge	Level of Health System	Project Partners Implementation Support Activities
Ensure adequate supply of core equipment, medicine and logistics required for infection management in UH&FWCs	Prior to implementation of guidelines, adequate supply of essential drugs and equipment were not available at UH&FWCs	Sub-district	• The project provided interim support to the MOHFW to ensure core items were available in the upazila supply chains for disbursement at union level: o **Equipment:** Thermometer, infant weighing scale, safety box for disposal of sharp instruments, ARI timer, insulin syringe o **Medicine***:* Injectable gentamicin, oral amoxicillin pediatric drops o **Job aids***:* Algorithm, dose calculation chart, *saf kotha* flip chart (counseling on Maternal and Newborn Health (MNH) messages) o **Reporting tools***:* sick newborn and young infant service register, prescription forms, referral note, FPI surveillance forms
		Union	• Collaborated with MOHFW throughout program period to fill gaps in supply of core items at UH&FWC
Capacity building of health workers to manage infections in young infants	Providers involved in implementation did not have previous training on PSBI management	National/ District/ Sub-district	• Training in PSBI management followed a cascade approach from the national to sub-district level. A pool of master trainers (MTs) were selected from district and sub-district level managers, in both DGHS and DGFP, and trained at the national level by a core trainer group. • Supported the MOHFW to strengthen the quality of care for sick infants at the referral facilities, which included training of clinical providers on PSBI management; emergency triage, assessment and treatment (ETAT); and functioning of Special Care Newborn Units (SCANU) at district level facilities for the advance care of critical cases

Component of Implementation Readiness	Challenge	Level of Health System	Project Partners Implementation Support Activities
		Sub-district & Union	• Provided 5-day training on PSBI management for 87 SACMOs including modules on the infection management guidelines o Organized an additional 2-day competency-based training focusing on completing registers and reporting forms (totaling 7-days of training) • Provided 2-day training to FWV on PSBI management, including provision of 2nd dose of injectable gentamicin in the absence of the SACMO
		Union	• Oriented FPIs (1-day) on home follow-up of PSBI cases receiving simplified antibiotic treatment
Supervision of health workers managing PSBI in young infants	Vacancies in MOHFW manager positions responsible for the supervision of UH&FWC providers	District	• In Lakshmipur, MaMoni HSS introduced a supervision and mentoring process to improve the quality of newborn care in the SCANU

		Sub-district	• In each of the 10 sub-districts a medical officer working at the UHC was identified by their DGHS supervisor (i.e., Civil Surgeon) and appointed as the Newborn Focal Point (NBFP)
			  o The NBFP, in coordination with the technical supervisor of DGFP (i.e., Medical Officer-MCH-FP), led the implementation of the PSBI management in their respective sub-district
			  o Led monthly meetings with SACMOs at the UHC, which served as a platform for program monitoring, monthly report preparation and refresher sessions of technical knowledge

Component of Implementation Readiness	Challenge	Level of Health System	Project Partners Implementation Support Activities
		Union	• Developed a supervision checklist for PSBI management through a consultation process with district and sub-district level managers. Sub-district managers used this checklist during onsite supervision visits at the UH&FWC • Performance on the checklist was reviewed monthly at the sub-district level and quarterly at district level • Project staff periodically joined MOHFW supervisors during visits to UH&FWC
Capacity building of CHWs in identification of newborn illness and referral	Promote new services available at UH&FWC	Ward/ Community	• Oriented Community Clinic staff (e.g., Community Health Care Providers [CHCP]) and GoB frontline workers (e.g., Family Welfare Assistant [FWA], Health Assistant [HA]) on identification of infant illness and appropriate sources of referral. Community Clinics (catchment area ~6,000 persons) are at the ward level and provide limited outpatient services. FWA and HA provide MNH messages during monthly home visits, ANC consultations, and bi-monthly satellites sessions for immunization and family planning services in the community.
		Union/ Community / Ward	• Print media, including billboards and posters, were placed in public places to disseminate newborn care messages, and broadcasted through local cable networks.

Component of Implementation Readiness	Challenge	Level of Health System	Project Partners Implementation Support Activities

Community mobilization and engagement of community groups	Delays in recognition of infant illness and prompt care-seeking from appropriate sources of care	Community / Ward	• In Lakshmipur, MaMoni HSS developed a pool of unpaid Community Volunteers (CV) (1 per 250 persons) who work as an extended arm of GoB frontline workers
			  ○ Oriented CVs on maternal and newborn danger signs and the process for community referrals
			• CVs facilitated a peer-led monthly community meeting to collect data on vital events and illness episodes (i.e., births, deaths, referrals, etc.)
			  ○ Shared data with the GoB CHW during their monthly community Microplanning Meetings (cMPM)
			• CVs recorded treatment outcomes for young infants with suspected infection that were treated at the UH&FWC

			• In Sylhet, Projahnmo oriented their existing cadre of program supported CHWs on the guidelines. During bimonthly home visits, CHWs promoted care-seeking from the public sector facilities when signs of illness were identified. • Projahnmo also oriented members of community groups (i.e., the local governing body for the Community Clinics) on newborn danger signs, the importance of care-seeking and the new services available at the UH&FWC.

Figure 1. Provision of public health services relevant to management of PSBI in young infants

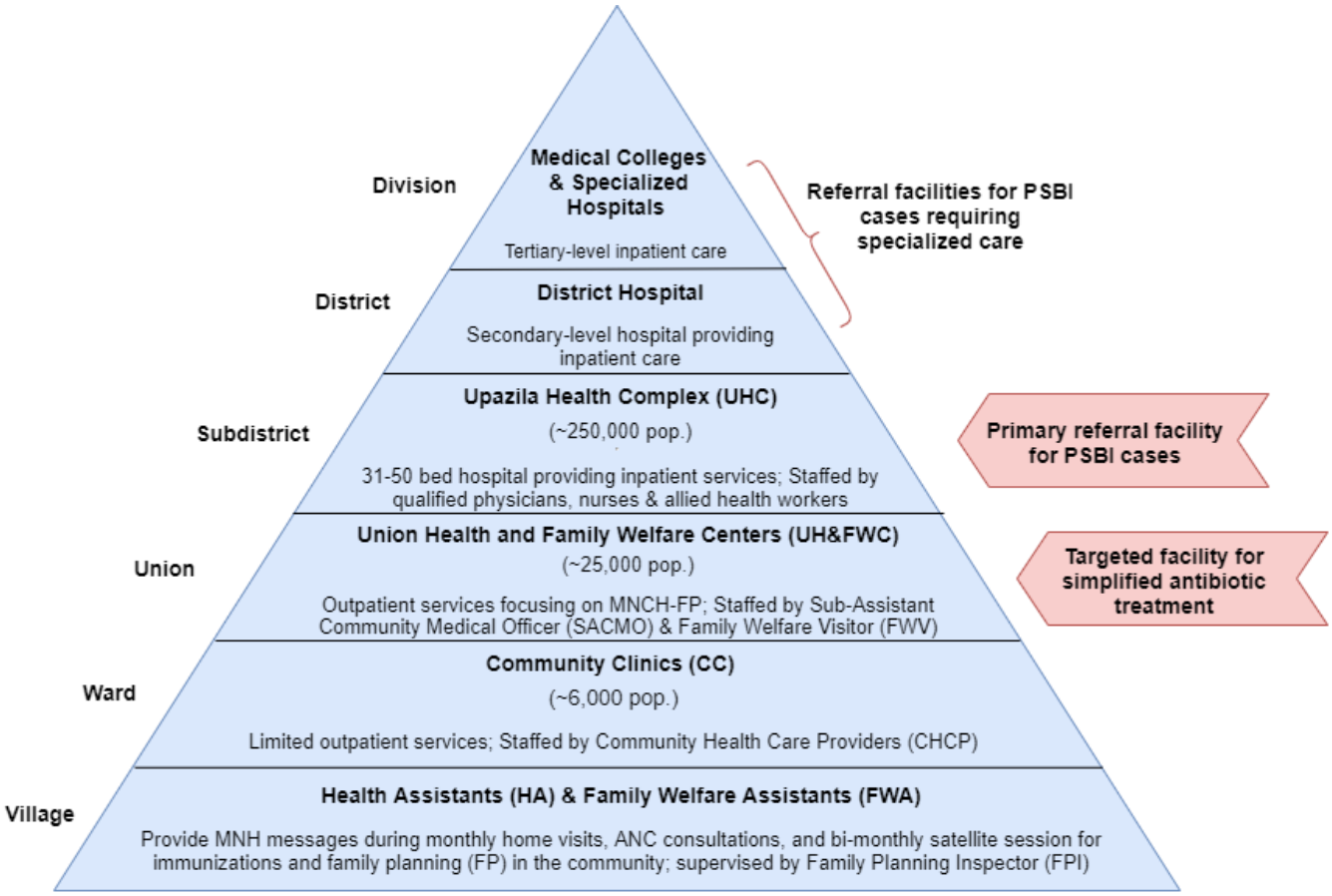
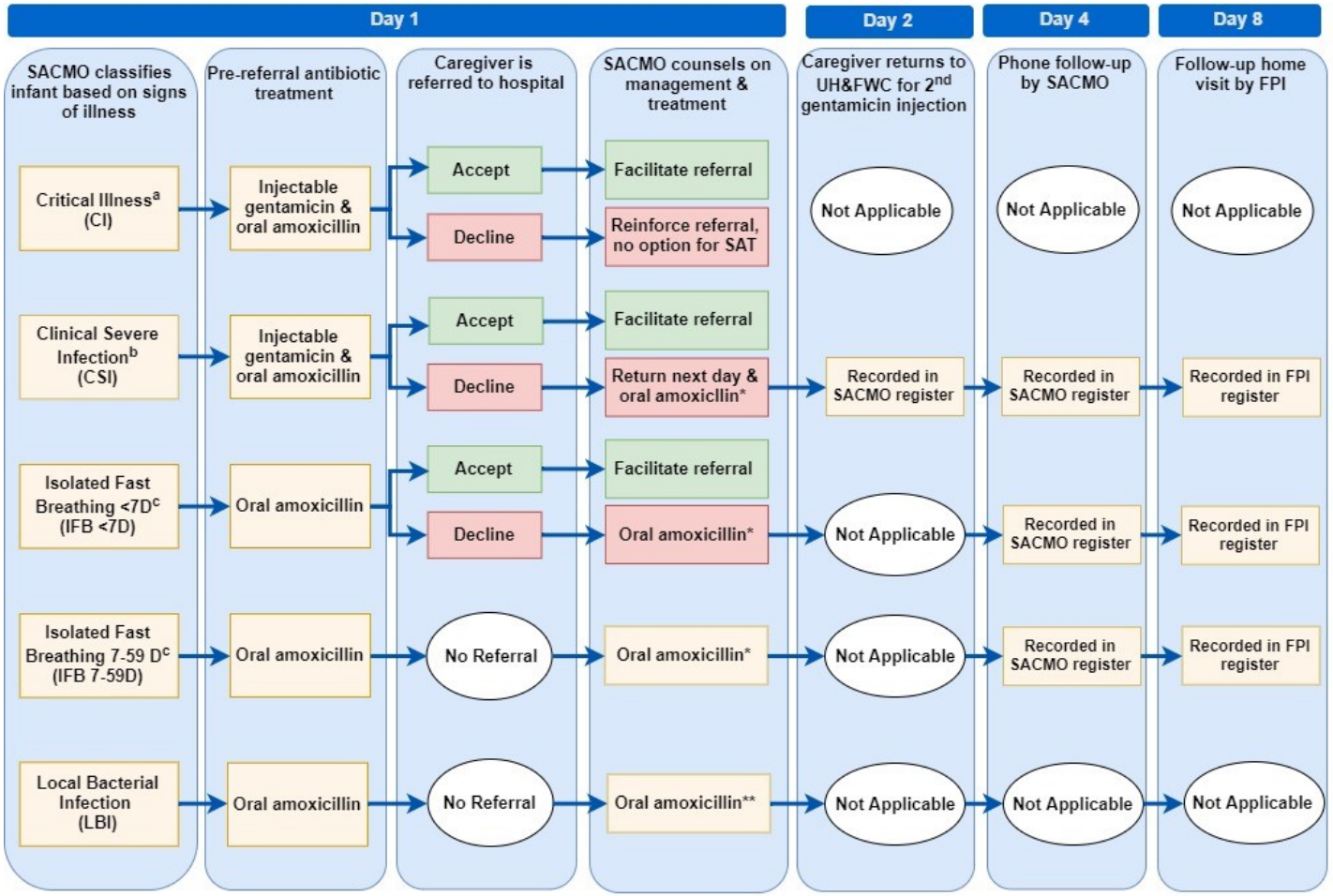


Figure 2. Management of the sick young infant at the UH&FWC per the Bangladesh infection management guidelines



[a] Critical Illness signs: unconscious, convulsions or history of convulsions, unable to feed at all, no movement on stimulation, unable to cry, persistent vomiting, bulging fontanelle, cyanosis

[b] Clinical Severe Infection signs: severe chest in-drawing, hypothermia (<35.5C), fever (>37.5C), movement only on stimulation, not feeding well (based on history and observation)

[c] Isolate Fast Breathing: respiratory rate equal to or greater than 60 breaths per minute as the single sign of infection

[d] Local Bacterial Infection signs: Umbilicus redness, draining pus from umbilicus, skin pustules

* The SACMO counsels the caregiver on providing medicine to the infant at home and prescribes oral amoxicillin twice daily for 7 days

** The SACMO counsels the caregiver on providing medicine to the infant at home and prescribes oral amoxicillin twice daily for 5 days

Chapter 3. Paper 1: Provider performance and facility readiness for managing infections in young infants in primary care facilities in rural Bangladesh

3.1 Abstract

Background: Neonatal infections remain a leading cause of newborn deaths globally. In 2015, WHO issued guidelines for managing possible serious bacterial infection (PSBI) in young infants (0-59 days) using simplified antibiotic regimens when compliance with hospital referral is not feasible. Bangladesh was one of the first countries to adopt WHO's guidelines for implementation. We report results of a prospective implementation research study that assessed facility readiness and provider performance in three rural sub-districts of Bangladesh during August 2015-August 2016.

Methods: This study took place in 19 primary health centers. Facility readiness was assessed using checklists completed by study staff at three time points. To assess provider performance, we extracted data for all infection cases from facility registers and compared providers' diagnosis and treatment against the guidelines. We plotted classification and dosage errors across the study period and superimposed a locally weighted smoothed (LOWESS) curve to analyze changes in performance over time. Focus group discussions (N=2) and in-depth interviews (N=28) with providers were conducted to identify barriers and facilitators for facility readiness and provider performance.

Results: At baseline, none of the facilities had adequate supply of antibiotics. During the 10-month period, 606 sick infants with signs of infection presented at the study facilities. Classification errors were identified in 14.9% (N=90/606) of records. For infants receiving the first dose(s) of antibiotic treatment (N=551), dosage errors were identified in 22.9% (N=126/551) of the records. Distribution of errors varied by facility (35.7% [IQR: 24.7-57.4%]) and infection severity. Errors were highest at the beginning of the study period and decreased over time.

Qualitative data suggest errors in early implementation may be due to providers learning new methods for assessment and treatment, confusion about classifying an infant with multiple signs of infection, and some providers' concerns about the efficacy of simplified antibiotic regimens. **Conclusion**: Clinical supervision and mentoring are important implementation supports when introducing complex guidelines in new settings. Strategies to monitor early performance and targeted supports are important for enhancing implementation fidelity. Future research should examine providers' assessment of effectiveness of simplified treatment and address misconceptions about superiority of broader spectrum antibiotics in treating community-acquired infections in young infants in this context.

3.2 Introduction

Bangladesh was among only a dozen lower-middle income countries to achieve the fourth Millennium Development Goal for child survival (1). Neonatal mortality, however, remains high (28 deaths per 1,000 livebirths). The slower annual rate of reduction in risk in this age group resulted in an increase as a proportion of all under-five deaths occurring in the neonatal period—from 44% in 1990 to 62% in 2015 (1-3). Newborn infections, including sepsis, meningitis and pneumonia, remain a major contributor to neonatal morbidity and mortality in this setting (4, 5). The signs and symptoms of neonatal sepsis are non-specific, which contributes to life-threatening delays in diagnosis and treatment, as newborns with severe infections can deteriorate rapidly if left untreated (6-8).

The World Health Organization (WHO) recommends that all young infants (0-59 days) with possible serious bacterial infections (PSBI) be referred to hospitals and treated with a 7 to 10-day course of a combination of two injectable antibiotics: gentamicin and either penicillin or ampicillin (9). In resource-limited settings, however, many infants with PSBI do not receive the recommended inpatient treatment (9, 10). In 2015, the WHO issued new guidelines for resource-limited settings for outpatient management of PSBI in young infants when hospital referral is not

feasible—including a clinical algorithm for classifying signs of PSBI and guidance on empiric treatment with antibiotics (9). The revised guidelines are based on systematic review of the evidence, including randomized trials conducted in South Asia and sub-Saharan Africa (11-13). These trials demonstrated that simplified antibiotic regimens—including fewer injections delivered by care providers closer to the community—resulted in similar rates of clinical failure as the standard more complicated regimen (11-13). Individual countries are expected to adopt the WHO recommendations and adapt implementation strategies based on their local social, economic, and cultural contexts (9, 14-16). Bangladesh was one of the first countries to adopt the WHO recommendations based on studies that showed these guidelines could help achieve 20% reduction in neonatal mortality (11, 15).

Bangladesh's primary health centers targeted for this intervention (i.e., Union Health & Family Welfare Centers [UH&FWC]; catchment area 25,000 persons) provide outpatient services, including essential health, nutrition and family planning services to mothers and children, and are generally staffed by providers with paramedic or medical assistant training in allopathic care (17-19). The designated provider for treating pediatric patients in these facilities are the Sub-Assistant Community Medical Officers (SACMO)—typically 1 SACMO per facility—following the Integrated Management of Childhood Illness (IMCI) protocol. Bangladesh's infection management guidelines will be integrated into the IMCI program, replacing the recommended protocol for young infants 0-2 months (9, 10, 20). In 1998, the government of Bangladesh (GoB) adopted the IMCI program as a strategy to reduce child mortality while improving the quality of care delivered at primary health facilities (21, 22). Evaluations of this related strategy identified that these facilities may not be well-equipped or supported to deliver IMCI services with notable gaps in provider performance, supervision and drugs (23-26). However, IMCI training combined with regular supportive supervision was found to improve quality of care in primary health facilities (24, 27, 28).

In 2015, the GoB partnered with funding agencies, implementation groups, and research organizations to operationalize the new guidelines in primary health care centers (15). Partner organizations undertook an implementation research study, following an adapted action learning cycle approach, or a Plan-Do-Study-Act (PDSA) approach, to assess early implementation and identify needed supports (29, 30). This study brought together a multidisciplinary stakeholder team to deliver a package of evidence-informed implementation strategies to support program rollout in rural primary health care centers (15, 31). Mixed methods data collection was embedded in study activities and lessons around implementation were shared with partners—including the GoB—in periodic stakeholder meetings (9, 10, 15). Adjustments to implementation strategies were made in real-time based on recommendations developed through these stakeholder meetings and following the PDSA approach (15, 29, 30).

As part of the implementation research study, we partnered with the Ministry of Health and Family Welfare (MOHFW) to support improvements in health facility readiness and capacity building of providers on the infection management guidelines in three rural sub-districts of Bangladesh during the first year of MOHFW-led program (August 2015-August 2016). In this paper, we present our implementation strategies and evaluation of *fidelity*—or the extent to which the intervention was implemented as intended in the original protocol (32). The objectives of this study were to: 1) assess facility readiness for managing infections in young infants at UH&FWCs over time; 2) assess provider performance on classification and providing the first dose(s) of antibiotic treatment over time; 3) to identify barriers and facilitators for facility readiness, provider performance, and quality of program delivery.

3.3 Methods

Context and Intervention

Bangladesh is divided into eight administrative divisions, which are further divided into districts and sub-districts. In rural areas, sub-districts are divided into unions, then into wards (3).

Our study area included union-level health centers in two sub-districts of Sylhet in Sylhet division and one sub-district in Lakshmipur in Chittagong division. Sylhet and Chittagong are historically low performing divisions of Bangladesh for maternal, newborn and child health indicators, including low rates of facility delivery and skilled attendants at birth (3).

Bangladesh's MOHFW is responsible for policymaking, while implementation of those policies is the responsibility of different directorate generals—Directorate General of Health Services (DGHS) and Directorate General of Family Planning (DGFP) are the two most important ones in terms of service delivery (17, 18, 33). The MOHFW maintains a three-tier system for delivering public healthcare services at all administrative levels and follows the IMCI protocol for management of sick children in primary health facilities (34, 35). Implementation of the infection management guidelines targeted union-level primary health facilities (i.e., UH&FWCs), which are generally staffed by 2-3 formally trained providers—the SACMO and the Family Welfare Visitor (FWV). Some of these facilities have a position for a doctor available, but these posts are often vacant (17, 18, 23). The SACMO has 3 years training on general healthcare, including child health, from a Government Medical Assistant Training School (17). The FWV has at least 18 months training from a private or government facility on midwifery and contraceptive management (17, 18, 34). In primary health care facilities, health services are highly subsidized by the government, requiring minimal or no payments from patients (18, 33).

The SACMO is the designated provider for assessing, classifying and treating young infants according to the adapted WHO guidelines. Most often, there is only one SACMO posted and available to treat pediatric patients at the UH&FWC. Thus, the individual knowledge and opinions of these provider will influence adoption and adherence to the guidelines. To aid these workers in identifying sick infants, the Bangladesh guidelines include a clinical algorithm for classifying signs of infection in young infants, guidance on antibiotic treatment, referral advice and follow-up (20). The algorithm is designed to have high sensitivity—as to not miss cases—

and includes seven signs of PSBI as well as other important signs of serious illness (Table 1) (9, 20, 36). If signs of infection are identified, then the SACMO classifies the infant as one of four sub-categories of infection—Critical Illness (CI), Clinical Severe Infection (CSI), Isolated Fast Breathing (IFB), or Local Bacterial Infection (LBI). Accordingly, the SACMO provides the first dose of antibiotics based on the infant's weight and refers the infants with signs of PSBI (i.e., CI, CSI, and very young infants [0-6 days] with IFB) to the sub-district hospital (Upazila Health Complex [UHC]; catchment area ~250,000 persons) for inpatient care (Table 1) (20, 34). If referral is not feasible for families, then the guidelines provide guidance on outpatient management of CSI and IFB cases with simplified antibiotic regimens. Hospital referral is the only option for critically ill infants. Fidelity as an implementation research outcome variable is typically measured by comparing the evidence-based intervention to actual implementation (32). Here, our analysis focuses on classification and pre-referral antibiotic treatment on the day of assessment by the SACMO at the UH&FWC. Henceforth, we will refer to SACMOs as "providers," UH&FWCs as "health centers," and the UHC as the "sub-district hospital."

Implementation strategies

This study was conducted as a part of partner support for early implementation of the PSBI guidelines in Bangladesh. Two non-governmental health programs— Projahnmo and MaMoni Health Systems Strengthening (HSS)—received USAID funding to support in a sample of health facilities in Sylhet and Lakshmipur districts. Projahnmo is a multi-institutional partnership including Johns Hopkins University (JHU), the MOHFW, International Centre for Diarrheal Disease Research, Bangladesh (icddr,b), Shimantik, and the Child Health Research Foundation (37). MaMoni HSS is a USAID-funded program to improve utilization of integrated maternal, newborn, child health, family planning and nutritional services (38). Henceforth, I will refer to Projahnmo and MaMoni HSS as "project partners."

Project partners' implementation strategies focused on improving readiness of targeted health centers to implement the guidelines and supporting the MOHFW to build capacity of providers. Health centers in the project areas were selected for targeted support based on the presence of a provider (e.g., SACMO) at the facility. Among the 31 health centers in the project areas within Sylhet and Lakshmipur, 12 were excluded because the SACMO post was vacant at the start of the study. The remaining 9 health centers in Zakiganj and Kanaighat sub-districts of Sylhet and 10 health centers in Ramganj sub-district of Lakshmipur received implementation support and were included in the implementation research study.

Prior to rollout of the guidelines, project partners identified gaps in the availability of intramuscular gentamicin, oral amoxicillin, and functioning equipment at study area health centers. After August 2015, the necessary commodities procured by the project were integrated into the existing supply chains and stocks were monitored throughout the study period to ensure against stockout. Project partners supported the government's training of supervisors and providers in the infection management guidelines following a cascade approach from the national to sub-district levels. Project partners also supported the distribution of registers, referral slips, and job aides to health centers. After August 2015, the guidelines were integrated into the both supervision sessions and project partners occasionally joined supervision sessions throughout the project period to improve the technical quality of these visits. However, partners did not provide inputs to increase the frequency of supervision. Stakeholder meetings were held in January 2016 and July 2016 to discuss program learnings after the initial rollout of the guidelines and study wrap-up respectively. Based on program monitoring data and sharing of learnings across study sites, project partners organized refresher trainings for providers in Sylhet (March 2016) and Lakshmipur (June 2016) to improve the quality of record keeping and provider adherence to the guidelines (Figure 1).

Design and Data Collection

This mixed methods study took place over a relatively short time period in order to inform the implementation of the PSBI guidelines nationally. As such, quantitative and qualitative data were collected concurrently following a convergent parallel design (39). Specifically, four data collection activities were undertaken: 1) a health facility checklist to assess readiness at baseline and over time; 2) weekly extraction of data from facility registers to monitor adherence to the guidelines for classification and treatment; 3) focus group discussions and 4) in-depth interviews with facility providers to identify facilitators and barriers to implementation (Figure 1). Data collection methods and measures are described by data source, below.

Health Facility Checklist: The health facility checklist, developed in collaboration with study partners based on the updated guidelines for infection management, focused on capturing health systems data on service-specific readiness (20, 40). Our team piloted the checklist in July 2015 and adapted questions prior to baseline data collection. The final checklist assessed the availability of the following requirements: 1) drugs for treatment of PSBI, including in injectable gentamicin and oral amoxicillin pediatric drops; 2) functioning equipment, including an infant scale and thermometer; 3) job aids developed for the PSBI guidelines; 4) facility infrastructure, including availability of electricity and clean water. The study team member completing the checklist physically observed and/or inspected relevant supplies and equipment on the checklist. Providers at each facility were also surveyed regarding the supervision that they had received and their participation in monthly meetings. The health facility checklist was administered at three points during the study period, six months after the start of implementation (March 2016) and then at the end of the study (August 2016).

Case management register review: To assess provider performance of the guidelines, we reviewed case data from a guideline-specific register. Register review was considered the most feasible method for assessing provider performance of the guidelines because the number of cases of PSBI at UH&FWCs is too small to facilitate assessment by direct observation assessments

(41). The young infant registers were developed specifically for the infection management guidelines and distributed to facilities as part of program rollout. Data collectors visited the 19 health centers weekly to abstract data from the records of all young infants that sought services from October 2015-August 2016. Our team adapted the register into an electronic form and recorded data weekly using tablets. For this analysis we included data on the infant's weight and body temperature, signs of illness, classification, and prescribed antibiotics and dosage.

Qualitative data collection: Both focus group discussions (FGDs) and in-depth interviews (IDIs) were conducted with SACMOs to assess their perceptions and acceptability of the guidelines using semi-structured interview guides. FGDs were conducted at the sub-district hospital on a date that coincided with the providers' monthly meetings or routine collection of medicines from this location. IDIs were conducted in the UH&FWC every 3-4 months during the study period.

All qualitative data collectors were Bangladeshi and conducted the FGDs and IDIs in the local language. Following each IDI and FGD, research assistants participated in debriefing sessions led by the research officers, to refine the guides and identify emerging themes for follow up during subsequent interviews (42). Interviews were recorded and transcribed into English by trained translators. Notes from the debriefing sessions were also translated into English and included in the analysis. All providers (N=19) trained in the guidelines and providing care in the study area were eligible to participate in the interviews. In the final months of data collection, follow-up interviews were conducted with providers for member checking of themes identified by the study team during analysis of interviews conducted during early implementation (43).

Ethics Statement

Ethical approval was obtained for this study from the Johns Hopkins Bloomberg School of Public Health Institutional Review Board (JHSPH IRB) and the Bangladesh Institute of Child Health (BICH) Review Board**.** Written informed consent was obtained for all study participants.

3.4 Analysis

Quantitative

Quantitative data were analyzed using Stata version 14 (StataCorp LP). We assessed the implementation readiness of the selected 19 health centers based on the health facility checklist. Our analysis of provider performance on practice outcomes—assessed by errors in classification and dosage—included all infants aged 0-59 days who presented with any signs of infection in the algorithm (20). We generated variables based on recorded measurement of the infant's body temperature, respiratory rate and weight to identify signs of illness in the algorithm including fever, hypothermia, fast breathing (respiratory rate ≥ 60 breaths/min), and weight <1500 grams. Records were excluded if date of assessment or signs of illness were missing. We developed and applied a computer algorithm to our record review to assess if the providers assigned the correct illness classification based on the signs of illness recorded. If the providers' classification did not agree with the algorithm, then we defined this as a *classification error*.

We defined appropriate antibiotic treatment as the infant receiving the correct dosage of injectable gentamicin and/or oral amoxicillin based on the infection classification per the algorithm. We estimated the correct dosage of injectable gentamicin and oral amoxicillin according to the national guidelines and using the dosage chart provided as job aides to the providers (Table 1). We used the infant's recorded weight to calculate the appropriate dose or dosage range. For oral amoxicillin, inappropriate dose was defined by if the infant received 20% more or less than the recommended dose, as has been used in previous studies (44, 45). We defined a *dosage error* as an incorrect amount of gentamicin and/or amoxicillin prescribed by the provider, or if the infant received treatment but their weight and/or antibiotic dosage were not recorded.

Descriptive results for both the health facility checklist and young infant records are summarized as frequencies, proportions, or as a median with the interquartile range (IQR). To

analyze changes in classification and treatment errors over time, we plotted the classification and dosage errors across the study period and superimposed a locally weighted smoothed (LOWESS) curve. We also examined variability in classification and dosage errors by facility/provider.

Qualitative

We adapted Damschoder's Consolidated Framework for Implementation Research to guide our analysis of qualitative data on determinants of feasibility, fidelity and provider acceptability of the guidelines (46). We employed an integrated approach to development of the coding framework (47). The framework was developed using *a priori* codes derived from the interview guides and the research questions related to feasibility, fidelity and acceptability of the guidelines. Emergent codes were added to the codebook as necessary to capture themes that were suggested in the data but not initially anticipated in the *a priori* codes. We coded transcripts using the computer software program Dedoose. This study employed analytical methods of continual analysis, coding, and memoing. To inform stakeholder meetings our team reviewed transcripts throughout the study period based on both inductive and deductive themes. After each study round, we adapted the questionnaire to explore emergent themes. Ultimately, we developed a coding framework—including a priori and emergent codes—based on continual review of the qualitative data. Each transcript was coded using this scheme and charting of the coded passages was used to facilitate interpretation of the data between two researchers.

Merged analysis of quantitative and qualitative data

After independent analysis of quantitative and qualitative data, we compared the strands based on dimensions of implementation readiness, healthcare providers' behaviors including the assessment and classification of young infants, and acceptability of simplified antibiotic regimen. Inferences were drawn for both quantitative and qualitative strands of data and then across strands to compare findings and develop recommendations for program scale-up (39).

3.5 Results

Our results are presented in three sub-sections, which report quantitative data from the health facility checklist and young infant records, and qualitative data from group discussions and interviews with providers to assess fidelity of the intervention through: 1) health center readiness and training of providers; 2) provider performance on practice outcomes (2a. classification and 2b. antibiotic treatment); 3) influence of implementation strategies on practice outcomes.

Health center readiness and training of providers

As described above, we excluded 38.7% (N=12/31) of health centers at baseline due to the provider's (i.e., SACMO) post being vacant at the time of study initiation. 19 health centers and providers from Sylhet (N=9) and Lakshmipur (N=10) were included in our analysis (Table 2). We conducted 2 group discussions with providers in the early months of the study (November and December 2015), 19 interviews during the study period, and 9 follow-up interviews in the final months of the study. Providers participated in every round of the health facility checklist and at least one interview during the study period. Most providers were male (84%; N=16). Time in their position varied from 1 to more than 20 years with nearly half of the providers serving 1-5 years in their current post (47%; N=9). 84.2% of the health centers (N=16/19) had the second health worker, the FWV, posted at baseline. Through group discussions and interviews, we learned that many of these providers also engaged in private practice, outside clinic hours, where they receive a fee for seeing patients and providing treatment.

All providers in our study received at least a 5-day training session on the infection management guidelines. When asked about training received, providers reported comprehension of the guidelines including the algorithm, referral process, and simplified antibiotic regimen. They appreciated the revised register format, which includes a visual depiction of the clinical algorithm, and described the job aides as helpful decision-making tools for classifying infection and calculating dosage. When probed on suggested improvements to the training sessions, in

interviews and group discussions, providers requested more "practical" demonstrations of a sick young infant visit. As one provider explained,

> *The demonstration that we watched on the computer screen. It could have been more effective we could watch a live demonstration… standing close to the patients... If we could see this for real by going to hospital, it would have been better.* –Provider in IDI

Prior to implementation of the guidelines, none of the study area facilities had injectable gentamicin available. Oral amoxicillin, as pediatric drops, was available at 79% of the facilities, but none had an adequate supply (Table 3). Availability of functioning equipment required for the assessment of infants, including a baby weighing scale, thermometer, and ARI timer or secondhand clock for measuring respiratory rate, were not universally available in the facilities. Project partners collaborated with the MOHFW and other stakeholders to supply drugs and equipment to the health centers beginning after August 2015. However, distribution of equipment was not instantaneous for all health centers as it had to be procured by project partners and integrated into existing supply channels. For example, some providers, in interviews and group discussions, described delays at study initiation for receiving digital weighing scales. All health centers received functioning equipment by December 2015.

Provider performance on practice outcomes: Classification and antibiotic treatment

Data on infant's age, weight, sex, signs of illness, infection classification, and antibiotic treatment were analyzed for 1,052 facility records. Records were excluded if date of assessment (N=2) or signs of illness (N=18) were missing. We also excluded young infants without signs of possible infection because they were not eligible to receive treatment according to the guidelines (N=426). Of these 426 records, 5 (1.2%) records were misclassified as IFB (N=2) and LBI (N=3), suggesting few infants were incorrectly classified with infection in the absence of signs from the clinical algorithm. Ultimately, 606 records from young infants with signs of infection were included in our analysis of provider performance (Table 4).

Nearly half of the infants (49%) were brought to the facility during the neonatal period (0-28 days). The signs of infection most frequently recorded in our sample included fast breathing (56%), umbilicus redness (19%) and fever (18%). The number of young infant records varied by health center with a median of 24 (IQR: 16.5 - 47) records per facility during the study period (Figure 2). The proportion of records with errors also varied by provider (1 per facility) with a median of 35.7% (IQR: 24.7-57.4%) per facility. When considering all errors in the records, we found that 3 providers contributed 39% of the total errors (Supplemental Table 1).

Provider performance on classifying young infants according to the algorithm

We identified classification errors in 14.9% (N=90) of the 606 infection cases. Records with signs of illness recorded, but missing classification contributed to 11.1% (N=10) of the classification errors. Providers correctly classified nearly all young infants with isolated fast breathing (97.7%; N=214/219) and local bacterial infection (97.7%; N=128/130), and 87% of young infants with critical illness (N=40/46) (Table 5). Providers' performance on classification was poorest for infants presenting with signs of clinical severe infection, with only 63.5% (N=134/211) of these infants classified correctly. These infants were frequently misclassified with less severe types of infection—including isolated fast breathing (N=31) and local bacterial infection (N=11)—or were missed completely and not treated according to the infection management protocol (N=24) (Supplemental Table 2). For infants with signs of clinical severe infection, but incorrectly classified, the presence of fever (>37.5C or 99.5F) was the illness sign most frequently missed by providers (74.0% [N=57/77]).

According to providers, in interviews and group discussions, implementation of the guidelines resulted in changes to their assessment practices for young infants, which may have contributed to errors in classification. For example, new strategies were introduced for measuring the infant's weight—using a digital versus mechanical scale—and measuring body temperature. As one provider noted, "Earlier we used to check temperature by thermometer for 1 minute

whereas it is now done for 3 minutes." Providers consistently mentioned young infant visits take longer, and assessment is more challenging compared to older pediatric patients. For example, one provider described difficulties measuring the infant's respiratory rate and body temperature,

> *When an ill baby comes it doesn't remain calm… then we face a problem in counting the baby's breathing. When we measure the temperature, we can't take the baby in our lap. The baby stays in its mother's lap. Then we face a problem because when we start measuring temperature the baby moves and cries*—Provider in interview

When probed on barriers to classifying infants according to the algorithm, some providers expressed confusion about assigning classification when the infant has multiple illness signs overlapping infection sub-categories. One provider reflected on a case illustrating this challenge,

> *A few days back, a newborn baby was brought to my [health center] with critical illness and he had clinical severe infection and local bacterial infection – three criteria were present in one baby. And along with this it had some other problems. In this case, what should I diagnose? —*Provider in interview

Provider performance on antibiotic treatment according to the dosage chart

For infants that received antibiotic treatment (N=551), we identified 149 errors in 22.9% (N=126) of the records for antibiotic dosage (N=106) or missing weight or dosage (n=43). We identified dosing errors in nearly one quarter of the gentamicin injections (23.7% [N=129/169]) and one fifth of the amoxicillin drops (19.8% [N=442/551]). When taken together, our analysis of practice outcomes indicates that only 23.9% of critical illness cases (N=11/46) and 44.5% of clinical severe infection cases (N=94/211) were correctly classified and received appropriate antibiotic treatment on the day of assessment at the health center. Providers performed better on classification and treatment of infants with isolated fast breathing (82.6%; N=181/219) and local bacterial infection (75.4%; N=98/130) (Table 5).

As discussed above, new practices for measuring the infant's weight and using the dosage chart, may have contributed to some of the errors in antibiotic dosing. However, we assessed antibiotic errors based on the recorded weight and dosage, so the errors we identified were likely due to miscalculations by providers either by mistake or because they did not agree with the

dosage chart. Prior to the new guidelines, providers were not authorized to treat young infants with PSBI in the public clinic (i.e., UH&FWC) when hospital referral was not feasible. However, some providers, in our group discussions and interviews, said they felt an ethical responsibility to treat these infants in their adjoining private practice when families were unable to seek care at the hospital. Therefore, they had previously established perceptions around *"*best practices*"* for treating young infants with serious infections. According to these providers, their preference was to treat sick infants with broader spectrum antibiotics (e.g., second or third generation cephalosporins) often prescribed at higher doses for a longer duration. As one provider discussed,

> *Before training, we used to prescribe high dosed antibiotics to little children…Now we see that rather than using high dosed antibiotics, the medicines we have learned about in the training, gentamicin and amoxicillin, are more effective with better results.*—Provider in group discussion

Providers, in interviews and group discussions, also discussed the introduction of the dosage chart to calculate the antibiotic dose based on the infant's weight. Some providers viewed this new practice as a positive change while others disagreed with the amount specified in the dosage chart,

> *The Amoxicillin drop that we used to use 3 times a day, now we use twice a day. And before that we used to use the dose in a different quantity and now the dose is given a certain quantity according to baby's weight…it is a positive change.* –Provider in interview

> *[Amoxicillin] needs to be measured based on the [infant's] weight how much drop is required to be given for 7 days. My personal idea doesn't match with the chart.* –Provider in group discussion

When probed on their opinions of the simplified antibiotic regimen, providers in interviews and group discussions expressed mixed perceptions of treatment efficacy. Providers that accepted and adopted the simplified regimen reported changing their prescribing behavior and highlighted the positives of the shorter course treatment, including cost-savings for families, and mothers' preferences for fewer injections. Other providers expressed concerns that simplified antibiotic regimens may be suboptimal for treating severe infections in young infants, which motivated

them to choose different courses of treatment, especially in their private practice. According to providers that did not agree with simplified treatment, they believe prescribing a higher number of doses of broad spectrum and newer generation antibiotics will result in quicker recovery time for patients. As one provider specified in an interview at the end of the study period, "If the babies get [oral antibiotic] of 3rd generation, they can recover earlier through a modern treatment." Providers often discussed pressure from caregivers and fear of losing patients as motivating factors for skipping recommended first-line treatment and opting for broad spectrum antibiotics. One provider explained his reasoning for starting antibiotic treatment with ceftriaxone—a third-generation cephalosporin recommended as a second-line antibiotic for treating neonatal sepsis (48)—due to fear of losing patients if sick infants do not recover quickly,

> *In the case of fast breathing we are supposed to give treatment only with amoxicillin. Here, in private chamber, we start with [ceftriaxone]. In private practice if one patient doesn't get cured, they go to another doctor… that's why we always want to give high dose treatment so that the patient gets well quickly.* –Provider in interview

These findings highlight some providers' misconceptions around appropriate antibiotic use, which could serve as potential barriers to adoption of the simplified antibiotic regimen.

Implementation pathway: Influence of implementation strategies on practice outcomes

To assess provider performance on practice outcomes over time, we plotted the classification and dosage errors across the study period. Based on this curve, we identified errors in classification and dosage were highest at the start of data collection and decreased over the study period (Figure 3). When we examined trends by infection sub-category, we found improvements in the providers' ability to classify signs of clinical severe infection and calculate oral amoxicillin dosage for infants with fast breathing were key drivers to reducing errors (Supplemental Figure 1). Qualitative data suggest that providers' performance improved as they gained practice with the guidelines and received feedback to improve recordkeeping and adherence in supervision and refresher training sessions (Table 6).

Providers had two opportunities for government supervision each month—onsite visits and monthly small group meetings led by government managers at the sub-district hospital. Monthly meetings at the sub-district hospital bring together all SACMOs in a subdistrict (~10 depending on the number of unions) and government managers. In addition to administrative activities (e.g., register review and completing reports), providers reported that these small group meetings provided an opportunity to discuss field implementation challenges with managers and served as group problem-solving sessions. Discussing the benefits of supervision, one provider said, *"*many things can be skipped or errors [made], by this inspection one benefit happens…our work gets more accurate*."* Most providers reported attending the monthly meetings at sub-district hospital regularly at baseline (78.9% [N=15]), midline (89.5% [N=17]), and endline (84.2% [N=16]) (Table 3). Onsite visits at the health center, however, occurred less frequently than planned with 42.1% - 63.2% of facilities reporting a visit in the previous 3 months (Table 3). 15.8% (N=3) of the providers reported not receiving an onsite supervisory visit in over one year. Providers attributed gaps in onsite supervision to lack of human resources at the manager level.

The first stakeholder meeting in Dhaka (January 2016) encouraged project partners to identify barriers to implementation, discuss early learnings with the GoB and other implementing partners, and develop local solutions. Recommendations from this meeting were integrated into subsequent supervision visits and shaped the agenda of refresher training sessions for providers (March and June 2016). For example, according to providers in interviews, confusion about overlapping signs of illness was addressed in both monthly supervision meetings and refresher trainings.

3.6 Discussion

This study presents implementation research findings on primary health centers' (i.e., UH&FWC) readiness and implementation fidelity for Bangladesh's infection management

guidelines throughout the first year of the program. Quantitative data indicate that providers' (i.e., SACMO) performance on the guidelines was high overall. When disaggregated by infection classification, however, infants with serious signs of infection were less likely to receive appropriate antibiotic treatment on the day of assessment due to combined errors in classification and dosage. However, providers' performance on the guidelines improved over the study period, particularly for classification of clinical severe infection cases and calculating dosage of oral amoxicillin. Qualitative data indicate that errors in the beginning of the study period may be due to delays in receiving essential commodities, introduction of new practices for assessment and calculating antibiotic dosage, providers' confusion about classifying an infant with multiple signs of infection, and providers' concerns about the efficacy of simplified antibiotic regimens. Multi-stakeholder collaboration to deliver implementation strategies improved facility readiness and may have accelerated improvements in provider performance on the guidelines. As the guidelines are scaled-up in Bangladesh, our findings highlight opportunities and recommendations for tailoring implementation strategies to improve health center readiness and fidelity of the program (Table 6).

Provider performance on classification was poorest for severe infection categories—critical illness and clinical severe infection—often resulting in lapses in pre-referral treatment with gentamicin. When combined with errors in antibiotic dosage, we found that only 23.9% (N=11/46) of critical illness cases and 44.5% (N=94/211) of clinical severe infection cases received appropriate antibiotic treatment on the day of assessment. Our findings are consistent with previous studies showing poor provider performance on the related IMCI guidelines contributed to misclassification of severe illness and lapses in treatment of infants and children (23-26). Classification of severe infection depends on the providers' ability to recognize and interpret subtle presentation of signs of PSBI, while less severe classifications are based on the absence of these signs (26, 49, 50). For example, we found 27% (N=57/211) of infants with signs

of clinical severe infection were incorrectly classified due to providers not recognizing the presence of fever in these infants. Since our study was limited to record review, we expect that classification errors were underestimated, particularly for severe illness cases requiring referral and treatment with gentamicin. Given the low number of cases and subtle presentation of signs of severe infection in young infants, emphasis on recognizing and interpreting the signs of PSBI should be prioritized in training and supervision to improve classification and subsequent management (49, 50).

A recent systematic review on effectiveness of strategies to improve healthcare provider practices in LMIC found packages of strategies—including training, group problem-solving and/or supervision, and providing job aides—were associated with larger improvements in provider performance than any of these strategies alone (51). Our study employed a similar package of implementation strategies to build capacity of provider and improve the technical quality of supervision. Trends in reduction of classification and dosage errors suggest that providers' performance on the guidelines improved as they gained practice with the guidelines. Errors in antibiotic dosage, however, declined at a slower rate than classification errors. During interviews, providers described the monthly supervision visits at the sub-district hospital as an opportunity for discussing field challenges and working with mangers to develop local solutions. Unlike errors in dosage, classification errors were identified as an early barrier during the study period and therefore were discussed during supervision and in-service training sessions, which may have accelerated decline of these errors. In areas suffering from severe health worker shortages, like rural Bangladesh (17, 52), our findings suggest monthly meetings could be used as a platform for mentoring providers to improve their technical knowledge of the guidelines and clinical skills. Furthermore, we found variations in provider performance with three facilities contributing 39% of the errors in our study area. Given human resource constraints limiting onsite supervision, targeting poor performing providers—especially early in program rollout—and

integrating case scenarios and practice with calculating antibiotic dosage may accelerate the learning curve.

Like many LMIC settings, ensuring appropriate access to antibiotics, while also avoiding excess use, is a major challenge in this context (53-55). Bangladesh has a high degree of antibiotic resistance, posing a global and regional threat, due to misuse and overuse of antibiotics in healthcare and agricultural sectors (56). Hospital-based studies of neonatal sepsis in South Asia report a high degree of resistance to important WHO-recommended first-line drugs (e.g., gentamicin and ampicillin) and third generation cephalosporins. Community-based studies of neonatal sepsis, however, have found low rates of resistance to these drugs allowing for effective outpatient treatment with first-line antibiotics in this context (48, 56-58). Our findings are consistent with previous studies that have identified irrational use and inappropriate prescribing of antibiotics by outpatient healthcare providers is common (56, 59-62). In interviews and group discussions, some providers related that simplified regimens are sub-optimal for treating severe infection, indicating their preference for higher doses of broader spectrum antibiotics to promote quicker recovery. Provider preference to begin treatment with higher doses of unnecessarily broad-spectrum antibiotics may result in higher drug costs for caregivers (limiting access) and promotes antibiotic resistance (through excess use). Steps to prevent misuse of antibiotics and preserve the effectiveness of first-line treatment in this setting will require interventions to restrict over-the-counter antibiotic use; engagement with the agricultural sector to reduce use in food animal production and pharmaceutical sector to curb aggressive marketing of broader spectrum, more expensive antibiotics; and improved surveillance systems (55, 56, 59). The revised guidelines, however, provide an opportunity to integrate antibiotic stewardship principles into training and supervision of outpatient providers to address misconceptions about the efficacy of simplified antibiotic regimens and target widespread irrational prescribing practices in Bangladesh's primary health facilities (59, 63, 64).

This mixed methods analysis presents data from early implementation of the guidelines, which is important for exploring contextual-specific challenges and data driven problem-solving. A key strength of this study is the use of both quantitative and qualitative approaches to provide a deeper understanding of the research questions than either method separately (39, 65). However, our study had several limitations including a short study period, lack of direct observations of care, and lack of a comparison group. Our study period was limited to one-year, which was necessary based on the government's plans for scale-up. The estimated incidence of PSBI in young infants (95.4/1000) in this setting, coupled with low care-seeking rates from this level of health facility, led us to expect few infants would seek care from study area public health facilities during the initial implementation period (3, 58). Thus, direct observations of care were not feasible, and we were limited to analysis of facility records. As a result, we were unable to measure providers' performance on clinical assessment including if any signs of infections were missed or incorrectly indicated in the register. Additionally, the quantitative data presented in this analysis may be subject to reporting bias. We aimed to improve the validity of our data by reviewing registers on a weekly basis rather than aggregated data from monthly reports. Our analysis of trends in errors and qualitative data allowed us to explore possible reasons for poor provider performance, but we were unable to causally link implementation strategies to changes in practice outcomes due to lack of a comparison group. Despite these limitations, our study has identified important barriers to early implementation and recommendations for improving the quality of care to sick young infants at health centers.

Since the conclusion of our study, Bangladesh has incorporated the infection management guidelines into their current National Newborn Health Program as part of the 4th Health, Population and Nutrition Sector Program and secured the necessary budget for procurement of the essential drugs and equipment under this plan (35). While this policy provides the mechanism for procuring and supplying antibiotics to the targeted health centers, our

study findings suggest other potential challenges to the structure of healthcare provision, including shortages of health workers and poor facility infrastructure. For example, we had to exclude 38.7% (N=12/31) of the health centers at baseline because the SACMO post was vacant and 15.8% (N=3/19) of the included health centers did not have a FWV posted at study initiation. Furthermore, clean water is important for reconstituting the oral amoxicillin powder, but few health centers in our study area facilities had provision for clean water. It is possible that these factors had unmeasured effects on providers' motivation and performance, which should be investigated in future studies. Development partners should continue to monitor and advocate for facility strengthening as bottlenecks in supply chains and health worker vacancies threaten scale-up and sustainability of the program.

Quality of care is a broad construct that includes the structure of the healthcare provision, process of providing care, and outcomes of care (66). Our study provides important insights about the structure of healthcare provision in the health centers, provider performance on the guidelines on the day of assessment, and recommendations for improving fidelity of implementation in rural Bangladesh. Future studies should examine caregiver acceptability of the guidelines—including their relationship with providers and opinions of care received at the health centers—and treatment outcomes for young infants receiving simplified antibiotic regimen. Future program support to the guidelines should integrate our recommendations to strengthen supportive supervision, test strategies to improve rational prescribing practices, and address misconceptions about superiority of newer generation antibiotics in treating community-acquired infections in young infants in this context.

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3.8 Tables for Paper 1

Table 1. Infection classification according to the clinical algorithm and antibiotic treatment on the day of assessment

Infection Classification	Clinical signs per algorithm	Antibiotic treatment at health center on day of assessment
Critical Illnesses (CI)	• Convulsion/history of convulsion* • Unconscious/drowsy • Unable to feed • Persistent vomiting • Central Cyanosis • Bulging Fontanel • Weight <1500 gm	• Intramuscular gentamicin (5.0-7.5 mg/kg body weight) • Oral amoxicillin 50 mg /kg body weight (twice daily)
Clinical Severe Infection (CSI)	• Severe chest in-drawing* • Hypothermia (<95.9^{0}F or 35.5^{0}C)* • Raised temperature (>99.5^{0}F or 37.5^{0}C)* • Less movement/ movement only when stimulated* • Not feeding well (depending on history and observation)*	• Intramuscular gentamicin (5.0-7.5 mg/kg body weight) • Oral amoxicillin 50 mg /kg body weight (twice daily)
Isolated Fast Breathing (IFB)	• Young infants 0-6 days old with fast breathing (≥60 breaths/min)*	• Oral amoxicillin 50 mg /kg body weight (twice daily)
	• Young infants 7-59 days old with fast breathing (≥60 breaths/min)	• Oral amoxicillin 50 mg /kg body weight (twice daily)
Local Bacterial Infection (LBI)	• Umbilical redness • Draining pus from umbilicus • Skin pustules	• Oral amoxicillin 50 mg /kg body weight (twice daily)
***Signs of PSBI requiring referral to sub-district hospital after first dose(s) of antibiotics (shaded boxes)**		

Table 2. Characteristics of the primary health facilities and providers in the sample

Characteristic	%(n) N=19
FACILITY	
District	
Sylhet	47% (9)
Lakshmipur	53% (10)
Managing Directorate	
Directorate General Health Services	53% (10)
Directorate General Family Planning	47% (9)
PROVIDER	
Sex	
Male	84% (16)
Female	16% (3)
Age	
20-29	16% (3)
30-39	11% (2)
40-49	0
50-59	42% (8)
Time in current posting	
1-5 years	47% (9)
5-10 years	16% (3)
10-15 years	5% (1)
15-20 years	21% (4)
>20 years	11% (2)

Table 3. Availability of core drugs and equipment at study area health centers for infection management and frequency of supervision visits throughout the study period (N=19)

Characteristics %(n)	Date of Assessment		
	August 2015	*March 2016*	*August 2016*
Drug supply			
Injectable gentamicin	0	100% (19)	100% (19)
- **Adequate supply**	0	89.5% (17)	100% (19)
Oral amoxicillin pediatric drops	78.9% (15)	94.7% (18)	100% (19)
- **Adequate supply**	0	94.4% (17)	100% (19)
Functioning Equipment			
Infant scale	47.4% (9)	100% (19)	100% (19)
Thermometer	10.5% (2)	84.2% (16)	100% (19)
ARI Timer/Watch	26.3% (5)	100% (19)	100% (19)
Job aides			
Algorithm visible during visit	0	84.2% (16)	100% (19)
Dose chart visible during visit	0	100% (19)	100% (19)
Infrastructure			
Clean water available	26.3% (5)	21.1% (4)	10.5% (2)
Electricity available	84% (16)	79% (15)	73.7% (14)
- **Uninterrupted in last week**	5% (1)	0	0
Supervision			
Government supervision in previous 3 months	63.2% (12)	42.1% (8)	63.2% (12)
- **Discussed infection management**	50% (6)	100% (8)	100% (12)
Attended monthly meeting	78.9% (15)	89.5% (17)	84.2% (16)
- **Discussed infection management**	33.3% (5)	94.1% (16)	100% (16)

***Based on day of assessment**

Table 4. Descriptive characteristics of sick young infants assessed at health centers

Characteristic	% (n) N=606
Age (in days)	
<7 days	9.7% (59)
7-28 days	39.1% (237)
29-59 days	51.2% (310)
Sex of infant	
Male	53.3% (323)
Female	46.7% (283)
Signs of illness recorded by provider	
Respiratory rate ≥60/min	55.8% (338)
Umbilicus redness	19% (115)
Fever (>37.5C)	17.8% (108)
Severe chest in-drawing	14.7% (89)
Not feeding well	13.5% (82)
Less movement than normal	6.1% (37)
Skin pustules	5.8% (35)
Hypothermia (<35.5C)	5% (30)
Unable to feed	4.3% (26)
Unconscious/Drowsy	3.3% (20)
Convulsions or history of convulsions	1.3% (8)
Persistent Vomiting	1.3% (8)
Weight<1500 g	0.8% (5)
Bulging fontanelle	0.5% (3)
Central cyanosis	0.5% (3)
Other signs	7.3% (44)

Table 5. Classification and treatment of young infants with signs of possible bacterial infection by providers

Classification (Computer Algorithm)	Correctly Classified by Provider %(n)	Antibiotic Treatment %(n)		Correct Antibiotic Dosage %(n)		Correctly Classified & Treated by Provider %(n)
		Gentamicin	*Amoxicillin*	*Gentamicin*	*Amoxicillin*	
Critical Illness (CI) (N=46)	87.0% (40)	71.7% (33)	73.9% (34)	52.2% (24)	39.1% (18)	23.9% (11)
Clinical Severe Infection (CSI) (N=211)	63.5% (134)	64.5% (136)	83.9% (177)	49.8% (105)	67.3% (142)	44.5% (94)
Isolated Fast Breathing (IFB) (N=219)	97.7% (214)	N/A	98.6% (216)	N/A	84.0% (184)	82.6% (181)
Local Bacterial Infection (LBI) (N=130)	97.7% (128)	N/A	95.4% (124)	N/A	75.4% (98)	75.4% (98)
Total (N=606)	85.1% (516)	65.8% (169)	90.9% (551)	50.2% (129)	72.9% (442)	63.4% (384)

Table 6. Results of qualitative investigation into reasons for high and low values of health facility readiness indicators and practice outcomes

Quantitative Results	Qualitative Themes		Recommendations
	Facilitators	***Barriers***	
Health center readiness and capacity building			
Study area health centers did not have adequate supply of injectable gentamicin nor oral amoxicillin and 89.5% did not have functioning equipment at baseline.	- Guidelines provided a discrete list of commodities (e.g., antibiotics, syringes, equipment) that should be provided to health centers which required minimal inputs from project partners for procurement and distribution to sub-district level stores.	- Distribution of drugs and equipment was not instantaneous as it was being integrated into existing supply chains from the sub-district level, which may have contributed to early errors in classification and treatment.	- The MOHFW has incorporated plans for training providers under the recent National Newborn Health Program and there is provision in the budget for drugs and equipment. As guidelines are scaled-up, development partners may continue to support rollout of the guidelines in health center to ensure readiness and promote sustainability.
Government supervision visits to health centers were infrequent during the study period, whereas at least 79% of provider reported attending monthly meetings at the sub-district level	- Providers discussed receiving benefits from supervision - Monthly meetings served as small group mentoring sessions to discuss problems and develop local solutions	- Onsite government supervision is infrequent due to human resource constraints at the manager level	- Monthly meetings provide a regular opportunity for mentoring, which could include skills assessment and correction
Practice Outcomes: Classification & antibiotic treatment			
Providers correctly classified 85.1% (N=516/606) of the infection cases. 85.6% (N=77/90) of all classification errors were	- Providers report comprehension of the algorithm and appreciate	- Some SACMOs said they were unsure of how to classify infants when multiple signs of illness	- Training and supervision should include case scenarios incorporating challenges specific to assessment and classification

identified in infants presenting with signs of CSI. Fever was missed in 74% (N=57/77) of the CSI cases that were misclassified.	the job aides as decision-making tools - Providers requested additional training with practical demonstrations	were present and/or overlapped classifications - Assessment of a young infant is more complex and time-consuming than other pediatric patients	of young infants, coaching on communication with caregivers, and when possible direct observations of care
For infants that received antibiotic treatment (N=551), we identified 149 errors in 22.9% (N=126) of the records for antibiotic dosage (N=106) or missing weight or dosage (n=43).	- Guidelines provide instruction on outpatient treatment of infections in young infants, which was not available previously - Many providers report that they are satisfied with providing fewer medicines and fewer doses of first-line antibiotics	- New methods for calculating dosage with digital scales and the dosing chart required practice and time to learn - Some providers do not agree with the simplified treatment and think that higher or more frequent doses of more powerful antibiotics are better	- Training should include a module on rationale use of antibiotics in outpatient settings - Record review with dosage chart during supervision may aid in identification and correction of dosage errors.
Provider performance on the guidelines varied by facility with three facilities contributing 39% of the errors in our study area. Provider errors in classification and antibiotic dosage decreased over the study period, largely due to improvements in classifying CSI cases and calculating dosage of oral amoxicillin for IFB cases.	- SACMOs reported fewer challenges as they gained practice with the guidelines (algorithm, equipment, dosage chart) and received feedback in supervision and refresher trainings	- In follow-up interviews, at the end of the study period, some providers continued to report they believed more powerful antibiotics resulted in quicker recovery time and better met caregiver demands	- Refresher trainings and monthly meetings provide an opportunity to visually check records, identify and correct errors, and improve provider performance on the guidelines - Increased supervision in the beginning of rollout may accelerate the learning curve - Given human resource constraints limiting frequent supervision, targeting poor performing facilities for additional support could reduce the overall error rate.

Supplemental Table 1. Errors in classification and antibiotic dosage by facility

Facility Union	**Young infant records**	**Facility records with errors %(n)**			**Cumulative % errors in all records**
		Total	*Classification*	*Dosage*	
Facility A*†	59	55.9 (33)	11.9 (7)	50.8 (30)	17.1
Facility B †	53	50.9 (27)	39.6 (21)	11.3 (6)	12.5
Facility C †	86	24.4 (21)	2.3 (2)	22.1 (19)	9.7
Facility D*	22	77.3 (17)	54.5 (12)	27.3 (6)	8.3
Facility E	57	26.3 (15)	19.3 (11)	7 (4)	6.9
Facility F	19	78.9 (15)	31.6 (6)	47.4 (9)	6.9
Facility G&	59	23.7 (14)	3.4 (2)	20.3 (12)	6.5
Facility H*	23	47.8 (11)	30.4 (7)	21.7 (5)	5.6
Facility I	36	25.0 (9)	19.4 (7)	5.6 (2)	4.2
Facility J	19	36.8 (7)	5.3 (1)	31.6 (6)	3.2
Facility K	11	63.6 (7)	0	63.6 (7)	3.2
Facility L	36	16.7 (6)	2.8 (1)	13.9 (5)	2.8
Facility M	24	25.0 (6)	16.7 (4)	8.3 (2)	2.8
Facility N*	14	28.6 (4)	28.6 (4)	7.1 (1)	2.3
Facility O	41	12.2 (5)	0	12.2 (5)	2.3
Facility P*&	4	75 (3)	75 (3)	25 (1)	1.9
Facility Q*	8	37.5 (3)	12.5 (1)	37.5 (3)	1.9
Facility R	6	33.3 (2)	16.7 (1)	16.7 (1)	0.9
Facility S&	29	6.9 (2)	0	6.9 (2)	0.9
Total	**606**	**35.6 (216)**	**14.9 (90)**	**22.9** (126)**	

*Denotes a facility that contributed records (N=9) containing both errors in classification and dosage
** Denominator for dosage errors is for infants that received antibiotic treatment (N=551)

Supplemental Table 2. Correct classification according to computer algorithm vs. classification recorded in the register

SACMO Classification	**Correct Classification based on Signs Recorded in Register**				
	CI	CSI	IFB	LBI	Total
CI	**40 (87.0 %)**	3	0	0	43
CSI	2	**134 (63.5%)**	2	0	138
IFB	1	31	**214 (97.7%)**	0	246
LBI	1	11	1	**128 (97.7%)**	141
Other	2	24	2	0	28
Missing classification	0	8	0	2	10
Total	**46**	**211**	**219**	**130**	**606**

3.9 Figures for Paper 1

Figure 1. Study timeline: Implementation strategies & data collection

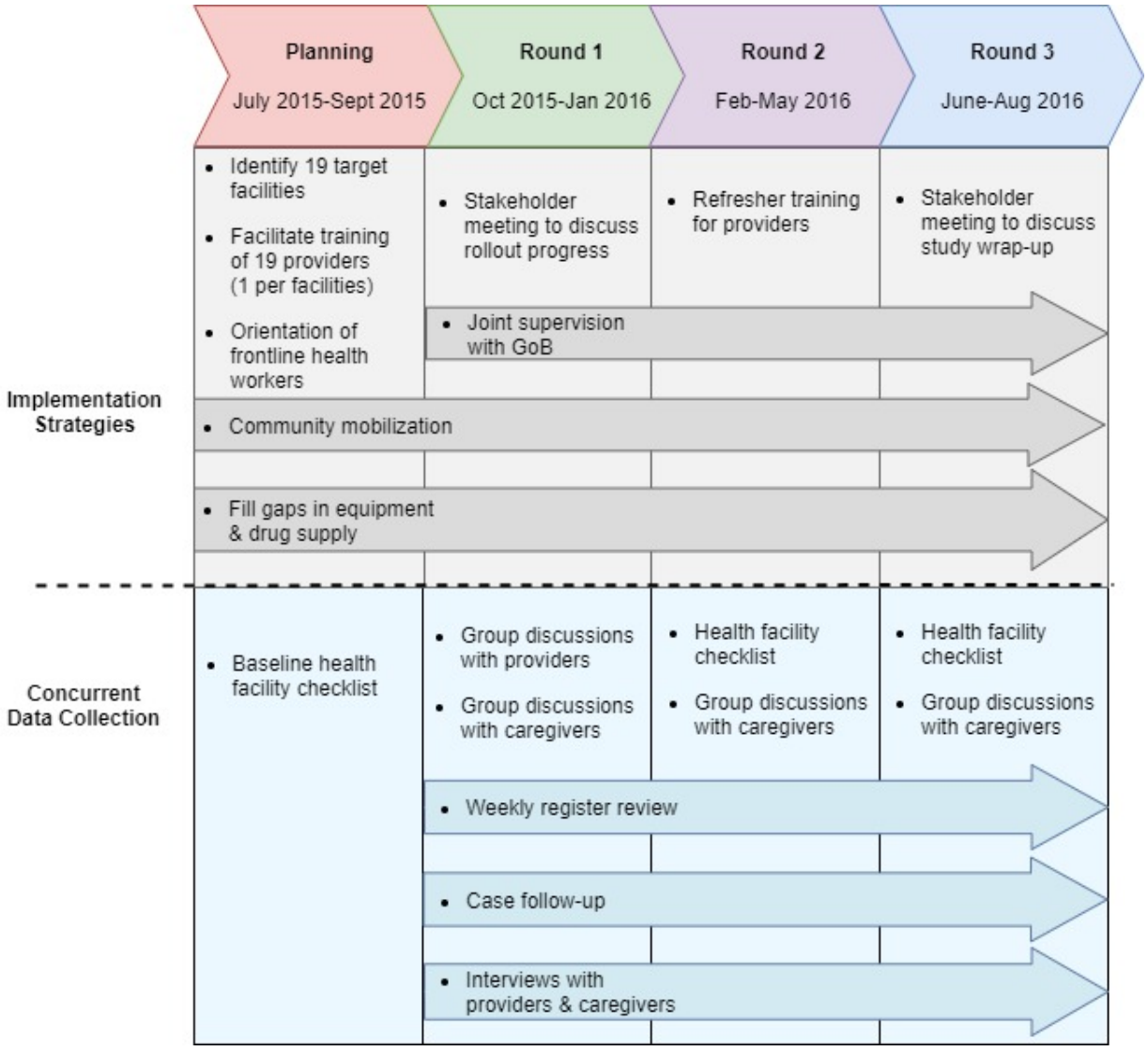


Figure 2. Distribution of young infant records and errors by health center

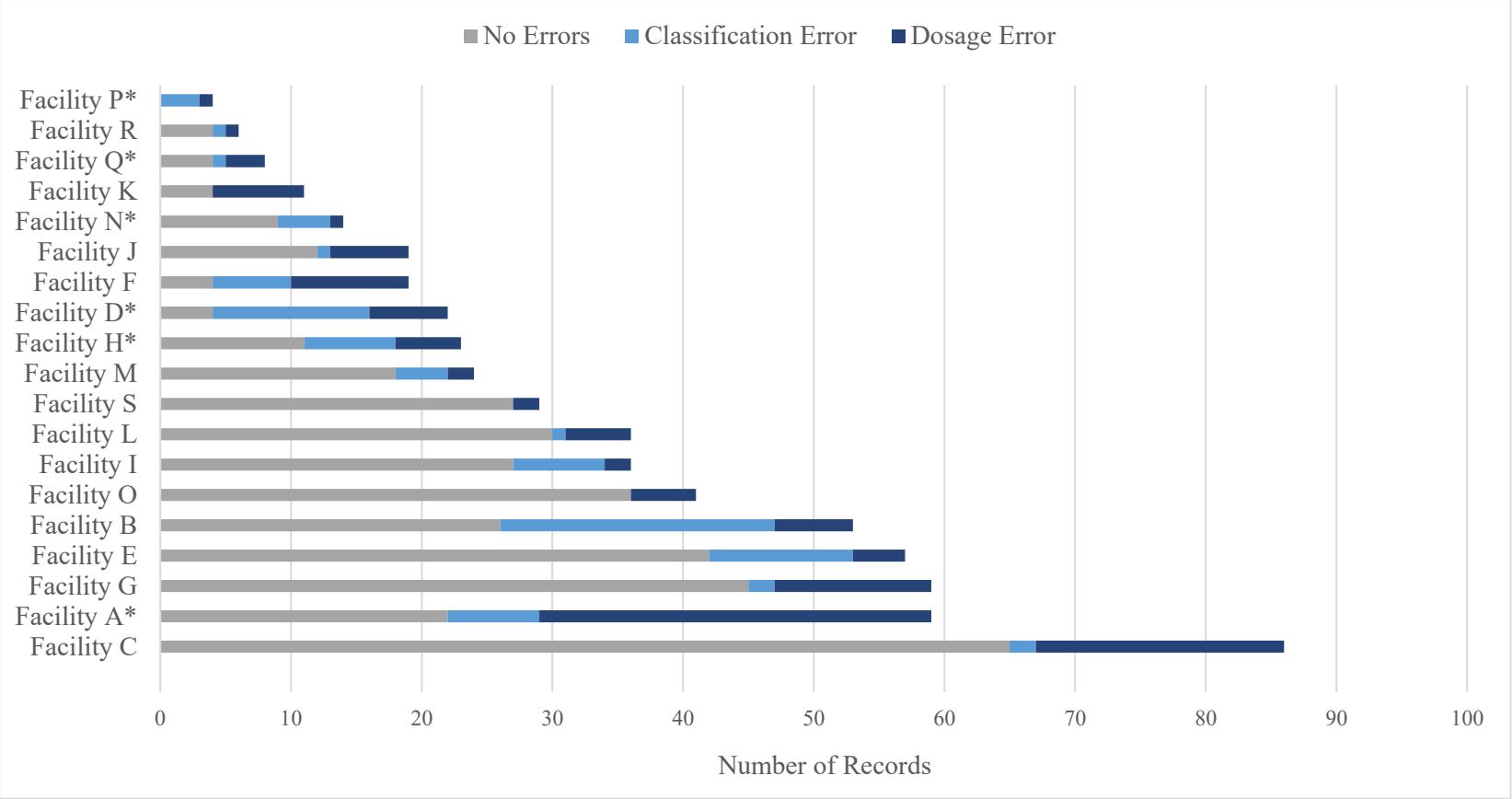
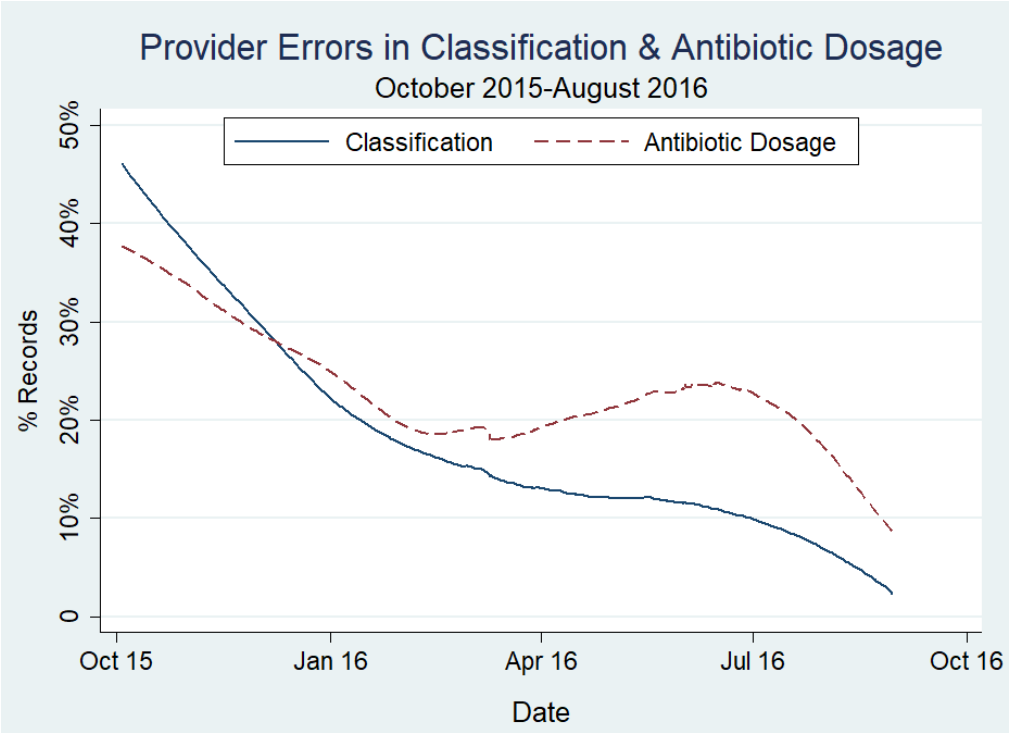
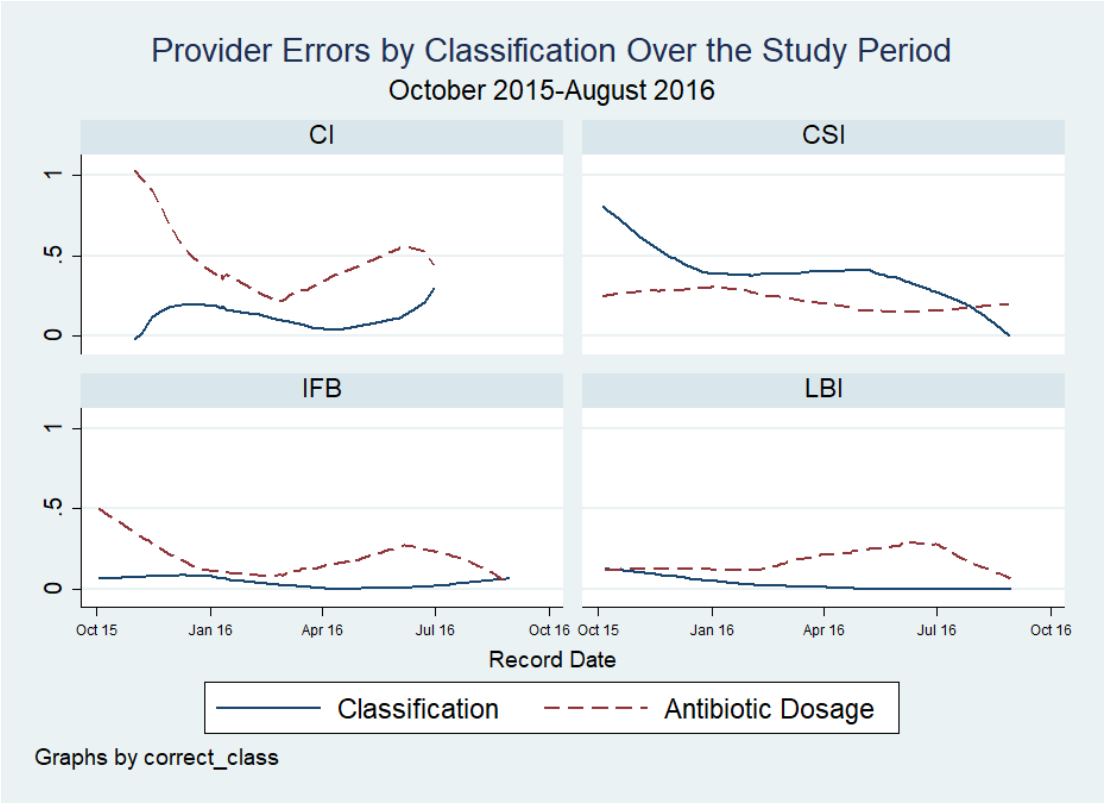


Figure Legend: *Denotes a facility that contributed records (N=9) containing both errors in classification and dosage

Figure 3. Provider errors in classification and treatment over the study period



Supplemental Figure 1. Provider errors in classification and treatment over the study period



Chapter 4. Paper 2: Caregiver acceptability of the guidelines for managing young infants with possible serious bacterial infections (PSBI) in primary care facilities in rural Bangladesh

4.1 Abstract

Introduction: Many infants with possible serious bacterial infections (PSBI) do not receive inpatient treatment because hospital care may not be affordable, accessible, or acceptable for families. In 2015, WHO issued guidelines for managing PSBI in young infants (0-59 days) with simpler antibiotic regimens at primary healthcare centers when hospital care is not feasible. Bangladesh adopted WHO's guidelines for implementation in outpatient primary healthcare facilities. We report results of an implementation research study that assessed caregiver acceptability of the guidelines in three rural sub-districts of Bangladesh during early implementation (October 2015-August 2016).

Methods: We included 19 outpatient primary health centers involved in the initial rollout of the infection management guidelines. We extracted data for all PSBI cases (N=192) from facility registers to identify gaps in referral feasibility, simplified antibiotic treatment and follow-up. Focus group discussions (FGD) and in-depth interviews (IDI) were conducted with both caregivers (6 FGDs; 23 IDIs) and providers (2 FGDs; 28 IDIs) to assess caregiver acceptability of the guidelines.

Results: Referral to the hospital was not feasible for many families (83.3%; N=160/192) and acceptance varied by infection severity. Barriers to referral feasibility included economic and household factors, and previous experiences with poor quality of care at the sub-district hospital. Conversely, providers and caregivers indicated high acceptability of simplified antibiotic treatment. 80% (N=96/120) of infants with clinical severe infection for whom referral was not feasible returned to the facility for the second antibiotic injection. Some providers reported

developing local solutions—including engaging informal providers in treatment of the infant—to address organizational barriers and promote treatment compliance. Follow-up of young infants receiving simplified treatment is critical, but only 67.4% (N=87/129) of infants received fourth day follow-up. Some providers' reported deviations from the guidelines that shifted responsibility of follow-up to the caregiver, which may have contributed to lapses.

Conclusion: Caregivers' perception of trust and communication with providers were influential in caregiver acceptability of care. Few caregivers accepted referral to the sub-district hospital, suggesting low acceptability of this option. When referral was not feasible, many caregivers reported satisfaction with simplified antibiotic treatment. Local solutions described by providers require further examination in this context to assess the safety and potential value of these strategies in outpatient treatment. Our findings suggest strengthening providers' interpersonal skills could improve caregiver acceptability of the guidelines.

4.2 Introduction

Bangladesh has made tremendous progress in reducing sepsis-related deaths during the neonatal period. Between 1990 and 2015, newborn deaths due to sepsis reduced by more than half, which is largely attributable to interventions to prevent and manage community-acquired newborn infections in this context, including promotion of clean delivery, essential newborn care practices and improved access to timely treatment with antibiotics (1-6). However, implementing these interventions at scale is challenging, resulting in sub-optimal coverage (7). As a result, newborn infections—including sepsis, meningitis and pneumonia—remain a major contributor to neonatal morbidity and mortality in Bangladesh and globally (1, 8, 9).

The World Health Organization (WHO) recommends that all young infants (0-59 days) with possible serious bacterial infections (PSBI) be referred to hospitals and treated with a 7 to 10-day course of a combination of gentamicin and either penicillin or ampicillin (10). In resource-limited settings, however, many infants with PSBI may not receive the recommended in-

patient care due to limited access to hospital facilities, social and cultural practices that may impede care-seeking, financial constraints and low acceptability of hospital care (10-13). The revised guidelines provide guidance on outpatient management of PSBI in young infants with simplified antibiotic regimens—including fewer injections combined with oral antibiotics—at primary healthcare facilities closer to the community (10).

Bangladesh was one of the first countries to adopt the WHO recommendations (14). In 2015, the government of Bangladesh partnered with funding agencies, implementation groups, and research organizations to operationalize the guidelines in primary health facilities in a few selected districts (14). A mixed methods implementation research study was embedded in program rollout to document lessons around implementation and inform nationwide scale-up. The updated infection management guidelines aim to increase coverage of treatment for newborn infections through provision of public sector care that more affordable, accessible, and acceptable for families (10, 11, 15).

In Bangladesh, health care is sought from a mix of sources including public and private providers in both the formal and informal sector, as well as traditional medicine (16-18). Rural and disadvantaged populations in Bangladesh commonly first seek care from a wide array of informal providers including village doctors, traditional healers, drug sellers, and homeopathic doctors (15, 16, 19, 20). Village doctors are prominent providers in rural communities—approximately 12.5 per 10,000 population. Most village doctors have limited or no standard training and are connected to unlicensed pharmacies where they diagnose patients and sell prescription medicines (15, 16). Public healthcare is highly subsidized by the government, requiring minimal or no payments from the clients, especially in the outpatient centers targeted for this intervention (i.e., Union Health & Family Welfare Centers [UH&FWC]; catchment area ~25,000 persons) (21, 22). Despite adequate geographic distribution of these outpatient health centers, UH&FWCs have been largely under-utilized by the communities, and many were not fully functional due to staff shortages, insufficient equipment, poor infrastructure, unavailability

of water and electricity, and perceived low quality of care (16, 18, 23-25). Families often prefer to seek care from the private sector, informal and formal, due to convenience and acceptability services, but informal providers are highly unregulated and formal care comes at high out-of-pocket costs for families (15, 16, 21, 26). With the rollout of the new guidelines, there is an urgent need to strengthen existing public sector facilities to improve the quality of care and acceptability of health services for families of sick young infants.

The guidelines are not designed to replace hospital care, which remains the first-line treatment for PSBI and only treatment option for critically ill infants. Bangladesh's national referral system is designed so that patients move up through the pyramid of care, typically beginning at the community level—at the base of the pyramid— with referrals to a larger facility for more specialized care at the sub-district or district-level. Referral is necessary when a patient's condition requires management that supersedes the training and/or resources at the basic level of care (27). The optimal situation is for patients to receive appropriate care at the lowest level possible to conserve resources for the patient and health system (27, 28). However, complexities around referral feasibility are well-documented in the literature and barriers may vary by context (27, 29, 30). The infection management guidelines aim to improve accessibility and quality of care at lower levels of the pyramid when referral is not feasible. WHO also emphasizes the need to understand barriers to referral feasibility, strengthen referral linkages, and improve the quality of care at referral facilities (10, 11).

Previous analyses from our implementation research study provide insights about quality of care from the supply-side, including the structure of healthcare provision in the UH&FWCs (e.g., drug supply, infrastructure, number and training of providers), providers' performance on the guidelines over time, and recommendations to enhance implementation fidelity (Applegate, Paper 1). In this paper, we present mixed-method findings to assess caregiver acceptability of the infection management guidelines during early implementation (October 2015-August 2016). *Acceptability* as an implementation research outcome differs from the larger construct of

satisfaction in that it focuses on a particular intervention or treatment—rather than general service experience—and is typically measured based on different aspects of the intervention and through the perspective of various stakeholders (31). In the early stages of implementation, acceptability is an important precursor to adoption of an intervention and will likely affect penetration and sustainability in the later stages (31, 32). Previous studies have shown multiple measures are beneficial for assessing client acceptability of health interventions, understanding the interpersonal relationship between provider and client, and developing strategies to improve quality of care (24, 31, 33). We posit that multi-level factors will affect caregiver acceptability of the updated treatment guidelines. Thus, we explored caregiver acceptability through application of the socioecological model (SEM), which accounts for multiple levels of influence on behavior (Supplemental Table 1). Here, we discuss caregiver acceptability of the infection management guidelines through identifying gaps in care of PSBI cases and examine barriers and facilitators to acceptability from the perspective of providers and caregivers in three sub-districts of rural Bangladesh.

4.3 Methods

Context and Intervention

Details on the context and intervention for this study have been described previously (Applegate, Paper 1) Briefly, our study area included union-level health centers in two sub-districts of Sylhet in Sylhet division and one sub-district in Lakshmipur in Chittagong division. Sylhet and Chittagong are historically low performing divisions of Bangladesh for maternal, newborn and child health indicators (34).

The MOHFW maintains a three-tier system for delivering public healthcare services at all administrative levels and follows the Integrated Management Childhood Illness (IMCI) protocol for management of sick children in primary health facilities (19, 35). Implementation of the infection management guidelines targeted union-level primary health facilities (i.e., UH&FWCs),

which are generally staffed by 2-3 formally trained providers—the Sub-Assistant Community Medical Officer (SACMO) and the Family Welfare Visitor (FWV). Some of these facilities have a position for a doctor available, but these posts are often vacant (16, 18, 25). The SACMO has 3 years training on general healthcare, including child health, from a Government Medical Assistant Training School (16). The FWV has at least 18 months training from a private or government facility on midwifery and contraceptive management (16, 18, 19).

The SACMO is the designated provider for assessing, classifying and treating young infants according to the guidelines. To aid these workers in identifying sick infants, the Bangladesh guidelines include a clinical algorithm for classifying signs of infection in young infants, guidance on antibiotic treatment, referral advice and follow-up (22). Infants with signs of PSBI (fever, hypothermia, convulsions, respiratory rate ≥60 breaths per minute if infant is <7 days, severe chest in-drawing, no movement or movement only upon stimulation, feeding poorly or not feeding at all) are classified as Critical Illness (CI), Clinical Severe Infection (CSI), or Isolate fast breathing <7 days (IFB <7). Accordingly, the SACMO provides the first dose of antibiotics based on the infant's weight and refers the infants with signs of PSBI (i.e., CI, CSI, and IFB [<7D]) to the sub-district hospital (Upazila Health Complex [UHC]; catchment area ~250,000 persons) for inpatient care (19, 22). Young infants classified as CSI or IFB (<7D) whose families decline hospital referral are eligible for simplified antibiotic treatment with injectable gentamicin once daily for two days and oral amoxicillin twice daily for seven days. Hospital referral is the only option for critically ill infants. Caregivers of infants with CSI that decline referral are instructed to return to the UH&FWC the next day for the 2nd gentamicin injection. The FWV may provide the 2nd injection if the SACMO is not present at the UH&FWC. The SACMO follows-up with caregivers over telephone on the fourth day, and if the infant's condition has not improved, advises the caregivers to seek care at the UHC. On the eighth day of treatment, the family receives a home visit from the Family Planning Inspector (FPI), who are trained as supervisors of frontline workers, to assess treatment compliance and the condition of

the infant (22). Henceforth, we will refer to SACMOs as "providers," UH&FWCs as "health centers," and the UHC as the "sub-district hospital."

Design and Data Collection

Project partners—Projahnmo and MaMoni Health Systems Strengthening (HSS)—supported the MOHFW to implement the guidelines in 3 sub-districts of the selected districts, Sylhet and Lakshmipur respectively. Both implementation partners have extensive experience supporting maternal, newborn and child health (MNCH) interventions and health system strengthening in rural Bangladesh, which has been described previously (36, 37). The supportive inputs from these two partners primarily focused on improving the performance and capacity of health services, including collaborating with the MOHFW to ensure the implementation readiness of health centers to manage infections in young infants, and supporting training and supervision of providers.

Our study employed a mixed methods approach to data collection following a convergent parallel design where quantitative and qualitative data were collect concurrently (38). We adapted the SEM to inform the development of interview guides to examine caregivers' acceptability of key components of the intervention—decision to seek care and perception of public sector care, referral feasibility, simplified antibiotic treatment and follow-up (Figure 1). Specifically, three data collection activities were included: 1) weekly extraction of data from facility registers to monitor adherence to the guidelines for referral feasibility, simplified antibiotic treatment, and follow-up; 2) focus group discussions (FGD) and in-depth interviews (IDI) with facility provider; and 3) FGD and IDI with caregivers of infants to examine facilitators and barriers to caregiver acceptability of the infection management guidelines.

Case management register review: Data collectors visited the 19 UH&FWCs weekly to abstract data from facility records of all young infants that sought services from October 2015-August 2016. The young infant registers used by providers were developed specifically for the infection management guidelines and distributed to facilities as part of program rollout (22). Our

team adapted the register into an electronic form and recorded data weekly using tablets. For this analysis we included data on the infant's age, provider classification of illness, referral feasibility, antibiotic treatment and follow-up.

FGDs and IDIs with providers: FGDs and IDIs with providers were conducted in both study areas to assess their perceptions of acceptability of the guidelines using semi-structured interview guides. The goal of these interviews was to assess the facilitators and barriers to implementation of the guidelines in the health centers. FGDs were conducted at the sub-district hospital on a date that coincided with their monthly meetings or routine collection of medicines from this location. IDIs were conducted in the health center every 3-4 months during the study period. All providers (N=19) trained in the guidelines and providing care in the study area health centers were eligible to participate in the interviews. In the final months of data collection, follow-up interviews were conducted with providers to explore themes identified by the study team through the analysis of interviews conducted during early implementation.

FGDs and IDIs with caregivers: FGDs with caregivers aimed to explore motivators and barriers to care-seeking from primary health facilities including specific questions about their previous experiences with care. For group discussions, caregivers were selected through convenience sampling of mothers (13-49 yrs.) of infants under six months of age who were willing and able to share their experiences with care-seeking for infant illness. The number of participants for each focus group ranged from 6 to 8 mothers. When selecting caregivers for participation in the FGDs we originally tried to select caregivers of young infants (<2 months) since this age group is the focus of the intervention. However, we had difficulty recruiting mothers with infants in this age group because many women in rural Bangladesh predominantly spend their time at home the first two months postpartum, which limits their ability to join a group discussion in the community (20, 39). We adjusted our inclusion criteria to allow mothers of infant under 6 months of age to participate in the FGDs. The goal of FGDs was to obtain

community perceptions about young infant illness, patterns of care-seeking and perceptions of care provided in government facilities.

The study team used facility records to identify young infants for follow-up in the community and select caregivers for IDIs. Caregivers were purposively selected based on their infant's categorization of infection. We conducted in-depth interviews with caregivers of infants for each category of PSBI. However, we prioritized reaching a point of saturation for the clinical severe infection cases because these infants receive referral to the hospital and are eligible for simplified antibiotic treatment, including two gentamicin injections, when referral is not feasible for families. The goal of these interviews was to assess the facilitators and barriers to referral feasibility and simplified antibiotic treatment from the perception of caregivers of young infants receiving treatment according to the guidelines.

All qualitative researchers were Bangladeshi and conducted the FGDs and IDIs in the local language (Sylheti in Sylhet, and Bangla in Chittagong). Interviews were recorded and transcribed into English by trained translators for analysis. Following the interviews, research assistants also participated in debriefing sessions led by the research officers utilizing a thematic framework. Notes from these debriefing sessions were also translated into English and included in the analysis.

Ethics Statement

Ethical approval was obtained for this study from the Johns Hopkins Bloomberg School of Public Health Institutional Review Board (JHSPH IRB) and the Bangladesh Institute of Child Health (BICH) Review Board. Written informed consent was obtained from all providers in the study, while oral informed consent was obtained from caregivers. Verbal consent was chosen for caregivers due to low literacy rates in this population. JHSPH IRB and BICH reviewed and approved all consent procedures for this study.

4.4 Analysis

Quantitative

Quantitative data were analyzed using Stata version 14 (StataCorp LP). Records were excluded if date of assessment or illness classification were missing. Descriptive results are summarized as frequencies and proportions for referral feasibility, caregiver return to the health center for the second injection, and follow-up according to the guidelines. We estimated the percent of PSBI cases captured at service delivery points in our study area based on the expected annual number of births for both Sylhet and Chittagong Divisions (34) and incidence of PSBI in young infants (95.4/1000) (40) in this setting.

Qualitative

We employed an integrated approach to development of the coding framework (41). The framework was developed using *a priori* codes derived from the interview guides and the research questions related to acceptability of the guidelines and application of SEM. Emergent codes were added to the codebook as necessary to capture themes that were suggested in the data but not initially anticipated in the *a priori* codes. We coded transcripts using the computer software program Dedoose. This study employed analytical methods of continual analysis, coding, and memoing. Our team reviewed transcripts of respondents throughout the study period based on both inductive and deductive themes. We adapted the questionnaire to explore emergent themes (42). Ultimately, we developed a coding framework—including a priori and emergent codes—based on continual review of the qualitative data, which was used for the final analysis. Each transcript was coded using this scheme and charting of the coded passages was used to facilitate interpretation of the data between two researchers.

4.5 Results

Quantitative

We analyzed data on the infant's age and sex, infection classification, referral decision and antibiotic treatment for 1052 facility records. Records were excluded if date of assessment (N=2) or illness classification (N=99) were missing. We included records of young infants classified with PSBI (i.e., CI, CSI, IFB <7D) that required referral according to the guidelines (N=192) (Table 1). Based on expected PSBI incidence for young infants in this context, we estimated that only 16.3% [95% CI: 14.4, 18.5] of the expected cases sought care from the study area health centers from October 2015-August 2016. Referral to the hospital was not feasible for many families (83.3%; N=160/192) and acceptance varied by infection severity: CI (28%; N=12/43), CSI (14%; N=20/140), IFB <7D (0) (Figure 2). For infants classified with clinical severe infection receiving simplified antibiotic treatment, 80% (N=96/120) of caregivers returned to the facility for the second injection. When referral was not feasible for families, 68% (N=82/120) of infants with CSI and (56%; N=5/9) of very young infants with IFB received follow-up from the provider on the fourth day of treatment. Our quantitative results indicate that day 8 follow-up in the community by the FPI was low for both CSI (36%; N=43/140) and IFB (56%; N=5/9). No caregiver in our interviews reported receiving a day 8 follow-up visit from the FPI for their infant's illness episode so we were unable to assess caregiver acceptability of these visits.

Qualitative

We analyzed qualitative data from 6 FGDs, 3 in each study area, and 23 IDIs with caregivers to explore their perceptions of care provided to sick young infants at public primary health facilities (e.g., UH&FWC and UHC) and acceptability of the infection management guidelines. All mothers completing an interview received care for their young infant according to the infection management guidelines. To understand providers' perspective of care provision, we conducted 2 focus group discussions with providers in the early months of the study (November and December 2015), 19 interviews during the study period, and 9 follow-up interviews in the

final months of the study. All providers in the study area participated in at least one interview during the study period. Our qualitative findings are presented in four sub-sections: 1) decision to seek care and experience at public health centers; 2) referral feasibility for families of infants with PSBI; 3) simplified antibiotic regimen and caregiver return for second day injection; 4) follow-up on the fourth day for infants receiving outpatient treatment. Table 2 presents our mixed methods findings around acceptability for each component included in this analysis.

Decision to seek care and experience at public health centers

According to caregivers and providers, mothers' autonomy to seek care for their infant outside the home is limited, oftentimes she must first obtain the consent of her husband. As one mother noted, "I won't be able to go outside of home without my husband's permission." Rather, the decision about when and where to seek care for the infant was described as a collective process that frequently included the baby's mother, father and/or grandparents (maternal or paternal). Informal providers residing in the community, especially village doctors, were often cited by caregivers in group discussions and interviews as the first source of care because services are provided at a reduced cost (no consultation fee, shorter distance to travel, no wait times) and they have a good relationship with the family. Of the village doctor, one mother said, "He calls us by name, even our husbands. He is very familiar." Mothers in our study all sought care from a study area health center and frequently reported the village doctor as their source of referral due to severity of the illness (e.g., pneumonia, convulsions), or if the illness persisted after the village doctor's treatment. Economic factors (consultation fee, cost of medicines, travel costs) were key drivers in the family's decision to choose public versus private sector facilities.

Mothers in interviews and group discussions often reported choosing the union-level health centers versus the sub-district hospital when the health center was closer to the community and they trusted the provider—often referring to him or her by name. As one mother said in a group discussion, "We think the treatment [the] doctor provides is trustworthy. That's why we come to UH&FWC [health center]." According to mothers, in group discussions, the quality of

care at the government primary health centers can vary across visits and locations. Caregivers, in interviews and group discussions, mentioned organizational factors (e.g., inconsistent availability of providers, long wait-times, medicine stock-outs) for dissatisfaction with public sector services, but reported these barriers occurred less frequently at the union-level health centers than at the sub-district hospitals.

Providers acknowledged that the guidelines provide an opportunity to improve families' access to and affordability of treatment. As one provider noted in a group discussion,

> *In this treatment method, cost is minimal. Earlier, it was very difficult for a poor family to bear the treatment cost.* –Provider in group discussion

Mothers were aware that services and medicines at government hospitals should be free of cost, but some reported paying a "visit fee" ranging from 10-500 Taka (0.12 to 6.00 USD). One mother reported asking the provider about the fee, smiling as she recounted her story,

> *He said, 'We need money to bear the costs' I said, 'Sir, I thought it is government hospital. Why should I give you money?' He said, 'The government bears the cost of medicine only. There are some other costs too.' I said, 'Is it so? Sir, I don't have money with me today. I didn't know. I'll bring next time when I'll come. During the [follow-up] visit, I gave 50 Taka to Sir and said, 'Sir, please have it for tea.'* –Mother of sick young infant

Providers did not discuss requesting a visit fee or accepting payment from the caregivers seen outside their private practice. When discussing the caregivers' satisfaction with treatment, one provider in a group discussion said,

> *Being pleased they like to give us some money. But I tell them that this treatment is absolutely free for you. If any babies around you become ill, inform this news to them. Thus, we publicize.* —Provider in group discussion

Providers in interviews and group discussions said they regarded the revised guidelines as an opportunity to improve care-seeking from these health centers and encouraged caregivers to share their positive experiences with family members and others in the community.

Referral acceptance by families of infants with PSBI

Our analysis of health center records indicate referral to the sub-district hospital was not feasible for many families (83.3%; N=160/192). According to providers, in interviews and group discussions, caregivers do not comply with referral primarily due to cost, household responsibilities, requiring their husband's consent, and lack of understanding about the severity of the infant's condition. Providers in interviews also acknowledged families' past negative experiences at the sub-district hospital as an important barrier to referral feasibility. One provider noted,

> *There is lack of cordiality to provide service in the higher health care center. As a whole it is seen that they [families] have bitter experience. For these reasons they do not like to go there.* —Provider in interview

When probed on referral feasibility, caregivers of sick infants in interviews, acknowledged economic hardships associated with accepting referral, but insisted these factors would not stop them from seeking higher level care for serious illnesses (e.g., pneumonia). For example, one mother said,

> *He [SACMO] told me to take it [baby] to sub-district hospital, I agreed. I was ready to take any risk for my child. I didn't worry about money. But I wanted my baby to be well again.* – Mother of sick infant

Some caregivers, in interviews, reported not accepting referral or delays in reaching the referral facility because permission of their husband, mother, or mother-in-law was needed. More often caregivers, in interviews and group discussions, cited inconsistent availability of services and community distrust in government doctors as reasons for not accepting referral to the sub-district hospital. Specifically, mothers reported previous dissatisfaction with government hospital services when their expectations were not met due to doctors not being available during regular service hours, long wait times, high consultation fees, medicine stock-outs, and doctors "misbehaving." When discussing her experience seeking care for her infant at the sub-district hospital, one mother said,

> *Suppose they talk with us angrily, 'There is no medicine. Why have you come here? Government does not give us medicines.' When they tell us these, we get hurt. So we do not go.* – Mother of infant in group discussion

Caregivers, in group discussions and interviews, often referred to government hospital providers as "bad doctors." This label, however, was not assigned based on a perceived lack of technical knowledge or skills. Rather, mothers explained they considered them to be "bad doctors" because of their disrespectful demeanor. Caregivers, in one group discussion, voiced agreement when one mother explained,

> *The doctors at government hospitals have so mean behavior, they feel annoyed when visited, won't speak two words in place of one… But they are not bad as doctors. It is not like they don't have proper medical knowledge. I don't go to them for their behavior.* —Mother of infant in group discussion

Occasionally mothers accepting referral advice reported choosing to seek care from private hospitals instead of the government hospitals due to the perceived higher quality of care.

When probed on facilitating referral for the 16.7% (N=32/192) of PSBI cases whose families accepted, providers reported mixed perceptions of their responsibility to follow-up with these families. Providers, in interviews, often reported giving the family a referral slip, their phone number, and the address and phone number of the referral facility. Some providers, however, also reported calling the doctor at the referral facility to say the family was on the way, then later calling the family to ensure they reached the facility. In these cases, the provider reported knowing the outcome of the patient, although there is not a field to record the outcomes of referred cases in the register. Caregivers that accepted referral reported in interviews that they faced fewer delays at the sub-district hospital when the provider called ahead and felt their infant's health was valued when a provider—either the SACMO or FWV—called to check on the baby's condition.

Simplified antibiotic regimen and caregiver return for second day injection

Providers, in interviews and group discussions, highlighted the positives of the simplified antibiotic regimen for caregivers including mothers' preference for fewer injections and treatment

with oral antibiotics on an outpatient basis, cost-savings for families, and less time away from their household and other children. When comparing the simplified regimen to standard inpatient treatment, one provider noted,

> *No mother wants her child to be pricked again and again. The revolutionary thing here is one injection for two days.* – Provider in group discussion

According to providers, mothers do not return to for the second injection due to lack of knowledge about allopathic medicine which placed onus on the caregiver for "not understanding many things," being "superstitious," and having "fear of modern treatment." Specifically, providers cited caregiver concerns that the baby's symptoms are not serious enough to warrant the injection and fear that the baby's condition will worsen after receiving the injection. For example, one provider highlighted,

> *We have to make the mothers understand…They think that the child might die after taking injection… They actually don't know why [a] injection is being provided.* –Provider in interview

Caregivers, in interviews and group discussions, were cognizant of the value of modern medicine to treat the sick infant especially when *Ayurvedic*—or traditional medicine—had not worked. However, caregivers indicated a clear preference for oral antibiotics given at home versus injections provided at facilities. Some caregivers, in interviews, expressed not returning for the second injection because permission of the husband, mother or mother-in-law was not granted for the return visit and/or injection. Mothers also discussed fears around providing antibiotic injections to young infants and concerns that these medicines could weaken the baby. As one mother described,

> *They gave the injection and I returned home…After giving medicines it [baby] became weak. I thought it was the side effects of the injection*—Mother of sick young infant

Providers also discussed organizational barriers to the second day injection when the scheduled return visit occurred on a weekend, or when the provider would be absent from the facility due to other duties (e.g., training, supervision meeting at the sub-district hospital). In the provider's absence, the guidelines allow for the FWV to provide the second injection, but

providers reported this rarely occurred. Rather, some providers reported dispensing the gentamicin injection to the caregiver and requesting they take it to their village doctor to be "pushed," or writing a prescription to be purchased at an outside pharmacy. Some caregivers of clinical severe infection cases confirmed receiving this guidance from the provider and in these cases confirmed visiting a pharmacy, or the village doctor, to have the injection administered. Of the few caregivers that described this experience, some expressed favorable reactions to continuing care with their village doctor closer to their home, while others highlighted potential barriers to this strategy. For example, one mother described the delay she faced when instructed to obtain the second injection from an outside pharmacy,

> *[SACMO] advised me to take the 2nd dose of injection from any pharmacy on the 2nd day. The reason was that [SACMO] would be on training on that day…At first we went to pharmacy. They said they cannot give the injection. Then, going to the [Bazar], we got the injection from another pharmacy.* – Mother of sick infant in interview

When probed on strategies to improve acceptability of the guidelines, providers in interviews and group discussions, discussed the need for strengthen counseling and communication skills with caregivers to improve compliance with referral and return visits to the health center, and acknowledged that the counseling should include other family members.

Follow-up on the fourth day for infants receiving outpatient simplified antibiotic treatment

Follow-up of PSBI cases on the fourth day of simplified antibiotic regimen is critical to ensure safe and effective treatment (10). The Bangladesh National Guidelines specify this follow-up be initiated by phone between the provider and caregiver (22). Based on our review of records, we found about two-thirds (67.4%; N=87/129) of these infants received follow-up on the fourth day of treatment. Providers, in group discussion and interviews, agreed with the importance of this visit for monitoring the infant's recovery, but reported various strategies for completing this visit. Some providers reported in interviews that they did not agree with initiating follow-up over

the phone, but instead requested the family to return to the facility on the fourth day, or said they would travel to the family's home, so they can clinically assess the child. As one provider described,

> *Calling on 4th day to follow-up, I can't accept this. This is not right following-up over mobile phone. For example, a patient has arrived with low temperature if I don't check his temperature then how can I tell that his condition is improved or not? …So I tell them [families] to come directly rather than talking over phone.* —Provider in interview

When probed on the feasibility of families' return to the health center, providers stated that caregivers often comply. If the caregiver does not agree to return, then providers said they request the caregiver to call or the provider will initiate follow-up by phone. Occasionally, providers in interviews discussed requiring families to return on the fourth day to obtain the full course of oral amoxicillin. One provider discussed using this technique to promote caregiver compliance, "sometimes we state, 'Here is a file of medicine. Kindly come to see me on the 4th day and collect another file of medicine too'."

Caregivers of infants receiving outpatient treatment confirmed in interviews that they received varying instructions from the providers regarding follow-up on the fourth day of treatment including phone calls and return visits. Caregivers that participated in this follow-up reported returning to the health center or discussing the infant's condition with the SACMO or FWV over the phone. All caregivers that received follow-up were satisfied with this aspect of care. When probed on the content of the day 4 follow-up phone call, one mother recalled,

> *She asked me how was my baby, whether I have fed my baby medicine and whether the 2nd dose injection was administered…I liked the treatment of [SACMO] very much. In a short period, I got very good treatment.* —Mother in interview

Barriers to follow-up, according to caregivers in interviews, included the provider not initiating the phone call or the caregiver not being given the phone number of the provider. Caregivers said they appreciated the provider giving their mobile phone number and indicated they would call him/her directly when they had questions or to setup an appointment.

4.6 Discussion

This study aimed to explore acceptability of the infection management guidelines from the perception of caregivers and providers during the first year of implementation in primary health facilities in Bangladesh. Few caregivers accepted referral to the sub-district hospital, suggesting low acceptability of this option for continued care and reinforcing the value of the option for simplified antibiotic treatment. Caregivers indicate distrust in hospital doctors, inconsistent availability of medicines, and financial constraints as the primary barriers to referral feasibility. However, caregivers insisted they would seek higher level care, from either the public or private sector, when they believed the infants' illness was severe. Providers and caregivers indicated high acceptability of simplified antibiotic treatment for infants receiving outpatient treatment, which they attributed to caregiver preference for providing oral antibiotics at home versus continued parenteral treatment at the hospital, reduced medical and travel costs, and less time away from their household and other children. More than three-quarters of infants with clinical severe infection for whom referral was not feasible returned to the facility for the second injection. Providers and caregivers attributed gaps in antibiotic treatment to caregiver concerns around providing injections to young infants and unavailability of the provider. Some providers reported developing local solutions—including engaging village doctors in treatment of the infant—to address organizational barriers and promote treatment compliance. Follow-up of young infants receiving simplified treatment is critical for monitoring the safety of the regimen, but only about two-thirds of families received follow-up from the provider on the fourth day of treatment. Provider deviations from the guidelines (e.g., requesting the caregiver return to the facility or initiate the phone call to the provider) may have contributed to gaps in follow-up since the responsibility of communication was deferred from the provider to the caregivers. Mothers reported greater satisfaction with care when they had a good interpersonal relationship and communication with the provider. These findings suggest strengthening providers' interpersonal

skills—including training on counseling that is culturally sensitive—and reinforcing the responsibility of the provider to initiate and continue follow-up could improve compliance and acceptability of the guidelines.

Our findings indicate informal providers were the preferred first choice in care due to their ability to meet the caregivers' emotional and social needs, reliability in providing drugs, and accessibility. Our findings are consistent with other studies that have found village doctors as an important first source of care and referral in the community (15, 24, 26, 43). Caregivers and providers also discussed utilizing village doctors for administering the second injection when mothers were unable to return to the facility due to unavailability of the provider. In areas suffering from severe health worker shortages, like rural Bangladesh, engaging informal providers in referral and management of sick young infants may feasibly improve reach and acceptability of the guidelines for caregivers (15-17, 22). However, previous efforts to engage informal providers in health service delivery have encountered complex barriers to implementation including lack of appropriate training, high rates of inappropriate prescribing due to market influences, and the absence of regulation and monitoring systems (15, 24, 33, 44, 45). For example, one study assessing the feasibility of engaging village doctors to implement Community-based Integrated Management of Childhood Illness (C-IMCI) guidelines in rural Bangladesh found village doctors' knowledge could be improved and retained through training and routine supervision (15). Despite their increase in knowledge, however, village doctors still engaged in inappropriate prescribing practices for children—especially for antibiotics. Authors suggested inappropriate prescribing behavior was likely influenced by these practitioners' reliance on profits from drug sells and incentives from pharmaceutical companies, highlighting some of the complexities associated with these types of interventions (15). However, the role of village doctors as the predominate providers for the poor in this context cannot be ignored and our findings suggest they are already integrated in infection management practices for young infants in the community. Previous research has promoted public-private partnerships (PPP) to

improve nationwide coverage of emergency obstetric and newborn care in Bangladesh (46). Future studies are needed to examine the potential for engaging informal and formal private providers, including the potential for fostering public-private partnerships (PPP) in this context (15, 44, 45). Previous research has promoted PPP to improve nationwide coverage of emergency obstetric and newborn care in Bangladesh (46). Additionally, public sector providers' opinions around engaging with private providers as allies should be explored as this has previously been identified as a barrier to implementation of PPP (47).

Our findings suggest referral feasibility is complex for both the families and health system contributing to life-threatening delays in care. Previous research in rural Bangladesh found acceptance of hospital admission for infants with signs of clinical severe infection sub-district hospital outpatient department was less than 20% (48). Referral acceptance in our study was lower (14%) for infants with signs of clinical severe infection. Families with critically ill infants accepted referral more frequently than infants with less severe signs of PSBI, but acceptance was still low (28%), resulting in 72% (N=31/43) of critically ill infants not receiving continued treatment or seeking care from the private sector—formal or informal—despite knowing there would be additional out-of-pocket costs. Caregivers' previous experiences with disrespectful treatment by providers and inconsistent availability of medicines at sub-district hospitals negatively affected referral feasibility. A study with sub-district hospital providers in rural Bangladesh found more than one quarter of the respondents did not believe the sub-district hospital was the right place to manage sick newborns, so they preferred to refer the family to a higher-level facility (49). Strengthening care at public sector referral facilities is needed to promote high quality, timely care for young infants with PSBI requiring inpatient treatment. At the union-level, providers should provide referral slips and follow-up with families to ensure they reached the referral facility, but follow-up is not recorded in the register and cases are not routinely tracked. We found providers reported varying levels of motivation to facilitate referral as demonstrated by connecting with doctors at the sub-district hospital and following up with

families to ensure they reached the facility. The few caregivers that described this level of referral facilitation reported improved experiences with care at the hospital and felt their baby's health was valued. As the guidelines are scaled-up, future implementation activities should aim to improve the quality of care at sub-district hospitals, establish systems for tracking referral cases, and reinforce the union-level providers' role to follow-up with referred cases to ensure they reach the higher-level facility.

We found caregivers' perception of the interpersonal nature of care—including communication and trust in providers—were influential in caregivers' acceptability of simplified antibiotic treatment and follow-up. Familial and social factors also influenced caregivers' decision to accept referral and return for the second day injection. Our findings are consistent with previous studies on quality of care in Bangladesh echoing the challenges of achieving optimal care that meets both medical and psychosocial needs of the users (15, 24, 33, 50). Providers have suggested that improved training in counseling of caregivers, husbands and other influential family members may improve acceptability and compliance with return visits for the second injection. Some providers also discussed developing local solutions to improve treatment compliance and the technical quality of follow-up on the fourth day. It has been suggested by Proctor, that providers' ability to adapt an intervention for local use may increase its acceptability (31, 51). For example, in the case of fourth day follow-up, providers' request for families to return to the facility for a clinical visit may improve their acceptability of the guidelines. However, further research into the feasibility of this strategy is needed. Additionally, training and program feedback should reinforce the importance of giving the full dose of antibiotics on the day of assessment and responsibility of the provider to initiate follow-up on the fourth day (22).

This mixed methods analysis presents findings on acceptability of the guidelines and identifies barriers and facilitators to simplified treatment and referral feasibility. However, our study had several limitations including lack of direct observations of care. The estimated incidence of PSBI in young infants (95.4/1000) (40) in this setting, coupled with low care-seeking

rates from the primary health facilities, led us to expect few infants would seek care at the study area health centers during the initial implementation period. Thus, direct observations of care were not feasible, and we were limited to analysis of facility records and qualitative interviews to assess compliance with the guidelines. Our study did not include implementation support activities or data collection at the sub-district hospital (i.e., UHC)—the recommended referral facility. Thus, we do not have data from the referral facilities to assess referral compliance, quality of care provided, or treatment outcomes for families accepting referral. Given referral complexities identified in this study, we anticipate referral compliance to be lower than acceptance rates recorded in the union-level health center records. Future studies should include data collection at public sector referral facilities to better understand barriers to referral compliance, quality of care, and identify opportunities for strengthening management of newborn infections. The eighth day visit is important for assessing treatment compliance and outcomes of infants receiving simplified antibiotic treatment. However, few infants received the day 8 follow-up visit, which limited our ability to explore the acceptability and functionality of this visit in qualitative interviews. Future analyses should include interviews with health workers responsible for this visit (i.e., FPIs) and explore barriers to completion. Finally, we found very few infants aged 0-6 days with IFB sought care at study area health centers, which limited our ability to assess caregiver acceptability of simplified antibiotic treatment for these cases.

There is growing interest around the importance of client's perceived quality of care in facilities, including the components of respectful care, communication, and responsiveness of providers (52-55). Similar to other studies, we found caregivers' perceptions of quality of care influences care decisions and may be shaped by community, family and societal expectations and values (52, 55-57). The health provider and caregiver's interpersonal relationship influenced caregivers' acceptability of the guidelines—including compliance with referral and simplified antibiotic treatment—which may affect treatment outcomes. Future trainings of providers should discuss strategies for including influential family members in the infant's care, incorporate

culturally sensitive counseling messages (e.g., acknowledging caregiver fears around injections), and reinforce the responsibility of the provider to initiate follow-up communication (e.g., referred cases, fourth day phone call) with the caregiver. Local solutions described by providers in our study—including requesting caregivers return for a clinical visit on the fourth day and engaging village doctors in providing the second gentamicin injection—require further examination in this context to assess the safety and potential value of these strategies. Inconsistent tracking of referral cases and perceived poor quality of care from public sector facilities are major barriers to referral acceptability, especially for critically ill infants whom are not eligible for the simplified regimen. As the guidelines are scaled-up, future implementation activities should aim to improve the quality of care at sub-district hospitals and strengthen linkages between public sector primary health facilities at the union and sub-district levels to ensure seriously ill infants receive continued care.

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4.8 Tables for Paper 2

Table 1. Descriptive characteristics of sick young infants classified as PSBI at health centers

Characteristic	% (n) N=192
Age (in days)	
<7 days	27.6% (53)
7-28 days	28.7% (55)
29-59 days	43.7% (84)
Sex of infant	
Male	57.8% (111)
Female	42.2% (81)
Signs of illness recorded by SACMO	
Respiratory rate ≥60/min	52.1% (100)
Severe chest in-drawing	45.8% (88)
Not feeding well	42.2% (81)
Fever (>37.5C)	27.6% (53)
Less movement than normal	19.3% (37)
Unable to feed	12.5% (24)
Unconscious/Drowsy	9.9% (19)
Hypothermia (<35.5C)	6.3% (12)
Convulsions or history of convulsions	4.2% (8)
Persistent Vomiting	3.6% (7)
Umbilicus redness	2.1% (4)
Weight <1500 g	2.1% (4)
Bulging fontanelle	1.6% (3)
Central cyanosis	1.6% (3)
Other signs	0.5% (1)
Skin pustules	0% (0)

Table 2. Results of qualitative investigation into reasons for high and low values of caregiver acceptability for key components of the guidelines

Quantitative Results	**Qualitative Themes**		**Provider adaption to strategies**
	Facilitators	***Barriers***	
Decision to seek care and experience at the public health center			
Only 16.3% of the expected number of PSBI cases sought care from the study area health centers	- Caregivers reported seeking care from health centers when they had trust in the provider - Village doctors were often the first source of care and frequently reported as a source of referral to the health center when their treatment failed	- Previous negative experience with public sector care, including inconsistent availability of providers and lack of medicines, discouraged care-seeking	- Providers encouraged caregivers to publicize services available at health centers
Referral feasibility			
Referral was not feasible for 83.3% (N=160/192) of PSBI cases	- Providers and caregivers reported outpatient treatment with fewer injections and oral antibiotics was more affordable and acceptable than inpatient care	- Some caregivers reported not accepting referral because permission was not obtained from their husband, mother-in-law, or other influential family member - Providers and caregivers reported previous experiences with disrespectful care and inconsistent availability of medicines at the sub-district hospital	- Some providers called the sub-district hospital to advise the families were coming and followed-up with caregivers to check on the baby - Caregivers reported fewer delays and higher acceptability of care received when the provider called the hospital and followed-up on the baby

		discouraged future care-seeking from this facility	
16.7% (N=32/192) of PSBI cases families accepted referral	- Caregivers reported they would seek care if they believed the illness to be serious - Many providers reported giving caregivers referral slips and their phone numbers for follow-up	- Referral is not routinely tracked by providers or recorded in the registers, so these infants are more likely to be lost to follow-up	
Simplified treatment regimen and return for second day injection			
80% of infants with CSI for whom referral was not feasible returned to the health center for the for the second injection on the next day	- Simplified treatment was more affordable and acceptable for continued care than inpatient treatment	- Providers and caregivers reported caregivers did not return due to fear around injections, perceptions that the infant's illness did not warrant a return visit/second injection, or permission was not obtained from an influential family member - Logistical barriers posed a challenge to follow-up when the visit fell on a weekend or a day when the provider was unavailable due to absence or training	- When the provider knew it would not be possible for the caregiver to return the next day, often due to unavailability of provider, some providers gave the caregiver the gentamicin injection to be administered by the village doctor or instructed them to purchase it at the pharmacy
Fourth day follow-up for PSBI cases receiving simplified treatment			

67.4% (N=87/129) of PSBI cases receiving outpatient treatment received follow-up on the fourth day	- Some providers said they requested the caregivers to return to the facility on day 4 for clinical assessment and would call if the caregiver did not return	- Some providers reported not initiating follow-up, but relying on the caregivers to return to the facility or call if the baby's condition did not improve	- Some providers said they requested the caregivers to return to the facility on day 4 for clinical assessment and would call if the caregiver did not return - Some caregivers reported providing enough oral amoxicillin to the caregiver until day 4 and then requesting they return for the complete regimen (which is not advisable)

Supplemental Table 1. Adapted SEM to assess multiple levels of influence on caregiver acceptability of guidelines

Levels of influence	**Description**	**Constructs explored in the interviews**
Individual	Factors related to the caregivers' knowledge and perception of care provided per the guidelines including antibiotics and referral	Caregiver autonomy in decision-making to seek care and accept referral; caregiver perception of illness severity; previous experiences with care at public sector facilities
Interpersonal	The role and influence household factors and other key actors in healthcare decision-making	Influence of economic factors, household responsibilities, and family members in decision-making for the infant's care (e.g., husband, mother or mother-in-law, other family members)
Organizational	Care received at public sector health facility and relationship with providers	Availability and accessibility of public sector services and medicines; Caregiver relationship with the provider; Provider motivation to facilitate referral and follow-up
Community	Social and cultural values that motivate or impede acceptability of treatment per the guidelines	Social and cultural values that influence care-seeking in this context; community perceptions of public sector care

4.9 Figures for Paper 2

Figure 1. Adapted socioecological model for analysis of embedded mixed methods study to assess caregiver acceptability of key components of infection management guidelines

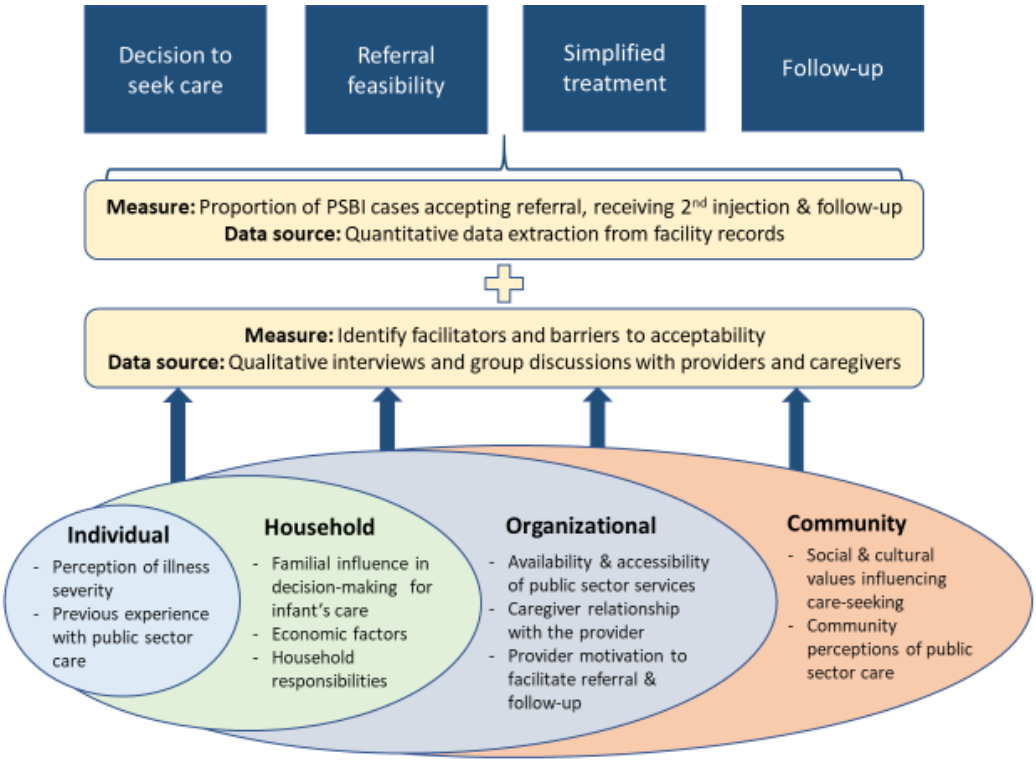
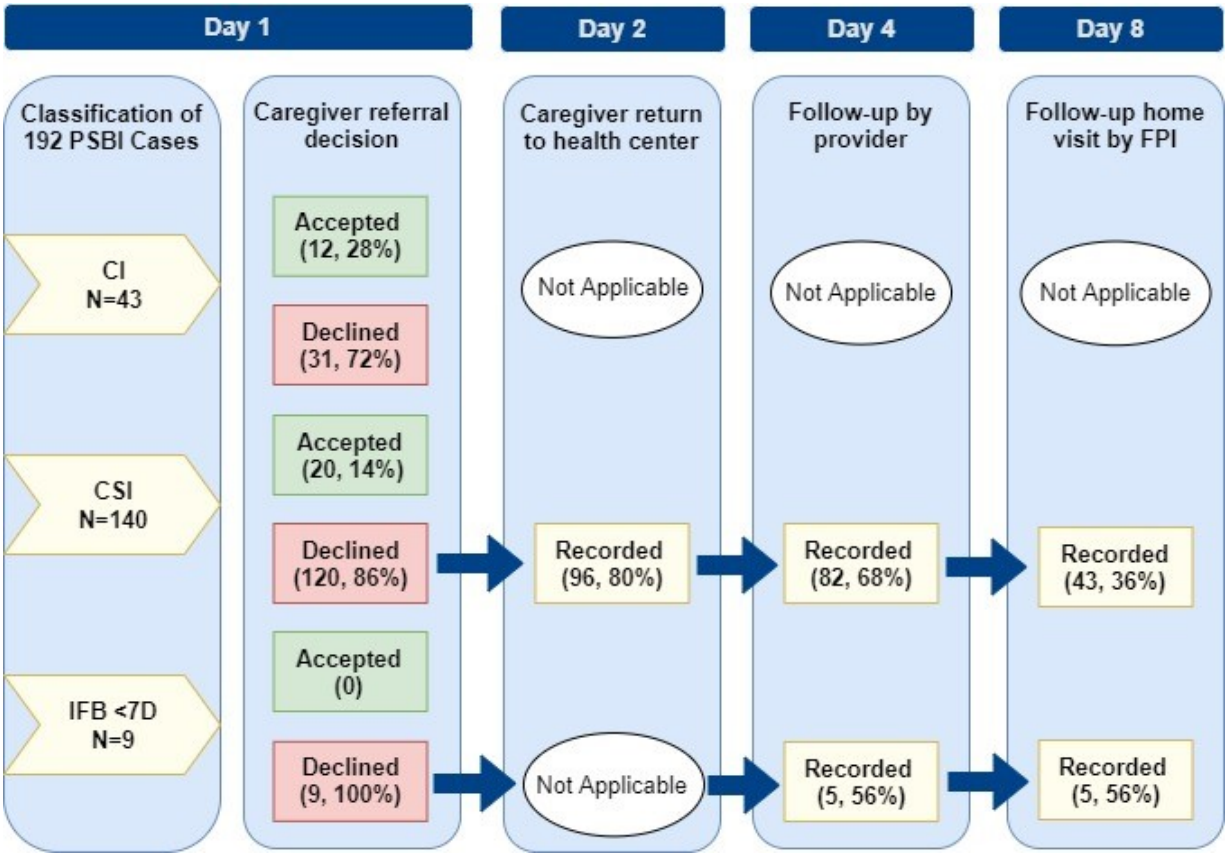


Figure 2. Management of PSBI cases that require referral and follow-up during the treatment period



Chapter 5. Paper 3: Patterns and determinants of caregiver non-adherence to oral amoxicillin for sick young infants receiving simplified antibiotic treatment

5.1 Abstract

Background: Infections remain a significant contributor to newborn morbidity and mortality. To increase access to treatment in resource-limited settings, WHO issued guidelines for managing possible serious bacterial infection (PSBI) in young infants (0-59 days) when hospital referral is not feasible for families. The simplified antibiotic regimen includes a critical home-based treatment component—oral amoxicillin twice daily for seven days. We report results from a mixed methods implementation research study that assessed patterns and determinants of caregiver non-adherence to oral amoxicillin in three rural sub-districts of Bangladesh during October 2015-August 2016.

Methods: This study took place in 19 primary health centers and catchment area communities. We extracted data for all infection cases from facility registers and followed-up families at their homes to assess caregiver-reported adherence with treatment through administration of a questionnaire. Adherence was defined as a categorical variable: 1) Adherent (10-14 doses); 2) Underuse (<10 doses); 3) Overuse (>14 doses). Bivariate analysis was conducted to examine associations between independent variables and adherence based on an adapted conceptual framework. Multivariable multinomial logistic regression was performed to examine selected factors with adherence adjusting for covariates. In-depth interviews (N=16) with caregivers were analyzed to identify barriers and facilitators to adherence.

Results: During the 10-month period, 229 caregivers of sick young infants reported they were responsible for giving oral amoxicillin to their sick infants. 62.4% of caregivers reported (N=143/299) administering 10-14 doses of oral amoxicillin to the infant during the illness episode, which we classified as adherent. 14.8% (N=34/229) of caregivers reported giving the

infant fewer than 10 doses at home, while 22.7% (N=52/229) of caregivers reported exceeding 14 doses of oral amoxicillin. Mothers that reported receiving follow-up from the provider during the illness period were less likely to provide fewer than ten doses (RR: 0.19; 95% CI: 0.05 – 0.74). While mothers that reported any barriers to giving oral antibiotics were more likely to provide fewer than ten doses (RR: 0.42; 95% CI: 0.22 – 0.78). No factors were associated with exceeding the recommended dosage. Qualitative data suggest caregivers had a better understanding of the regimen when the provider gave verbal and written instructions, marked the dropper to reflect the dosage amount and demonstrated giving the first dose. Caregivers reported skipping doses when the baby experienced side-effects to the medicine (e.g., vomiting), and would discontinue treatment if they believed the baby was no longer sick.

Conclusion: Provider counseling on continuing medicine and follow-up with sick infants is important for caregiver adherence to the oral amoxicillin regimen. Improving the quality of counseling to include messages on handling side-effects and reinforcing the need to complete the full course may improve adherence. Strategies are needed to improve provider adherence to the guidelines—including demonstrating the first dose and day 4 follow-up—as the guidelines are scaled-up nationwide.

5.2 Introduction

Appropriate case management of serious infections in newborns, including early identification and appropriate treatment with antibiotics, may result in a 24% reduction in infection-related neonatal deaths (1-4). In 2015, the World Health Organization (WHO) released new guidelines for managing young infants (0-59 days) with possible serious bacterial infections (PSBI) when hospital care is not feasible for families. The guidelines are based on systematic review of the evidence, including trials in sub-Saharan Africa and South Asia, which showed that simplified antibiotic treatment regimens—including fewer injections combined with oral amoxicillin—was as effective as the standard seven day course of a combination of gentamicin

and penicillin (5-9). The revised guidelines also changed recommendations for infants (7-59 days) with fast breathing as the only sign of illness based on findings that showed oral amoxicillin is equivalent in clinical effectiveness to parenteral therapy for these infants (8). These guidelines are intended for implementation in resource-limited settings where many infants with PSBI may not receive the recommended in-patient treatment (9-12). Bangladesh was one of the first countries to adopt the WHO recommendations (13). In 2015, the government of Bangladesh partnered with funding agencies, implementation groups, and research organizations to operationalize the guidelines in primary health facilities in a few selected districts (13). A mixed methods implementation research study was embedded in program rollout to document lessons around implementation and inform nationwide scale-up (9, 10, 14).

Simpler antibiotic regimens have been found to be associated with improved patient adherence, reduced misuse of antibiotics, and higher treatment acceptance by patients (15, 16). For infants with PSBI, the simplified antibiotic treatment regimen aims to improve access to care and includes a critical home-based treatment component with oral amoxicillin. Randomized controlled trials that contributed to the evidence of simplified treatment reported high treatment adherence for combination therapy regimens (5, 7, 8). However, since these were efficacy trials, well-trained study personnel were responsible for visiting the homes of infants and ensuring correct administration of the antibiotics. As part of the implementation research study, we aimed to study caregiver adherence to outpatient oral amoxicillin in the absence of study intervention.

Previous studies of ambulatory treatment of childhood illnesses, including pneumonia, with oral antibiotics report a wide range of caregiver adherence to antibiotic regimens—from 40%-97%— and primarily focus on treatment of children under-five years of age (17-20). With growing concerns about antibiotic resistance, there is an increasing focus in the adherence literature on rational use of antibiotics—including both underuse and overuse—in community settings (15, 16, 21-23). To our knowledge, this is first study assessing predictors, barriers and

facilitators to caregiver adherence to oral amoxicillin regimens for young infants receiving outpatient treatment according to the revised infection management guidelines in Bangladesh.

The caregivers' experience with administering antibiotics is an important contributor to acceptability and clinical effectiveness of outpatient treatment. Adherence to medication is complex and multi-faceted, making predicting non-adherence to medication difficult (24). WHO defines adherence as "the extent to which the persons' behavior, including medication-taking, corresponds with agreed recommendations from a healthcare provider" (25, 26). We utilized WHO's five dimensions of adherence as well as findings from previous studies to inform our conceptual framework for this study (Figure 1) (15, 16, 21, 25-27). Here, we discuss mixed methods study findings on caregiver adherence to oral antibiotic regimens including determinants of adherence and barrier and facilitators to home treatment.

5.2 Methods

Context and Intervention

Bangladesh is divided into eight administrative divisions, which are further divided into districts and sub-districts. In rural areas, sub-districts are divided into unions, then into wards (28). Our study area included union-level health centers in two sub-districts of Sylhet in Sylhet division and one sub-district in Lakshmipur in Chittagong division. Sylhet and Chittagong are historically low performing divisions of Bangladesh for maternal, newborn and child health indicators, including low rates of facility delivery and skilled attendants at birth (28).

The MOHFW maintains a three-tier system for delivering public healthcare services at all administrative levels and follows the Integrated Management Childhood Illness (IMCI) protocol for management of sick children in primary health facilities (29, 30). Implementation of the infection management guidelines targeted union-level primary health facilities (i.e., UH&FWCs), which are generally staffed by 2-3 formally trained providers—the Sub-Assistant Community Medical Officer (SACMO) and the Family Welfare Visitor (FWV). Some of these facilities have

a position for a doctor available, but these posts are often vacant (31-33). The SACMO has 3 years training on general healthcare, including child health, from a Government Medical Assistant Training School (31). The FWV has at least 18 months training from a private or government facility on midwifery and contraceptive management (29, 31, 33).

The SACMO is the designated provider for assessing, classifying and treating young infants according to the guidelines. To aid these workers in identifying sick infants, the Bangladesh guidelines include a clinical algorithm for classifying signs of infection in young infants, guidance on antibiotic treatment, referral advice and follow-up (34). Infants with signs of PSBI (fever, hypothermia, convulsions, respiratory rate ≥60 breaths per minute if infant is <7 days, severe chest in-drawing, no movement or movement only upon stimulation, feeding poorly or not feeding at all) are classified as Critical Illness (CI), Clinical Severe Infection (CSI), or Isolate Fast Breathing in infants aged 0-6 days (IFB <7). Accordingly, the SACMO provides the first dose of antibiotics based on the infant's weight and refers the infants with signs of PSBI (i.e., CI, CSI, and IFB [<7D]) to the sub-district hospital (Upazila Health Complex [UHC]; catchment area ~250,000 persons) for inpatient care (29, 34). Young infants classified as CSI or IFB (<7D) whose families decline hospital referral are eligible for simplified antibiotic treatment with injectable gentamicin once daily for two days and oral amoxicillin twice daily for seven days. Hospital referral is the only option for critically ill infants. Caregivers of infants with CSI that decline referral are instructed to return to the UH&FWC the next day for the 2nd gentamicin injection. The SACMO follows-up with caregivers over telephone on the fourth day, and if the infant's condition has not improved, advises the caregivers to seek care at the sub-district hospital. On the eighth day of treatment, the family receives a home visit from the Family Planning Inspector (FPI), who are trained as supervisors of frontline workers, to assess treatment compliance and the condition of the infant (34). Caregiver compliance with return visits and provider adherence to day 4 follow-up are reported elsewhere (Applegate, Paper 2). In this paper, we assessed caregiver adherence to the oral amoxicillin regimen—twice per day for seven days—

for infants receiving outpatient antibiotic treatment (e.g., CSI and IFB cases). As part of training on the updated PSBI guidelines, SACMOs received training on the importance of counseling caregivers on the oral antibiotic regimen and were instructed to ask about treatment compliance at the fourth day of treatment. Henceforth, we will refer to SACMOs as "providers" and the UH&FWCs as "health centers."

Design and Data Collection

Project partners—Projahnmo and MaMoni Health Systems Strengthening (HSS)—supported the MOHFW to implement the guidelines in 3 sub-districts of the selected districts, Sylhet and Lakshmipur respectively. Both implementation partners have extensive experience supporting maternal, newborn and child health (MNCH) interventions and health system strengthening in rural Bangladesh, which has been described previously (35, 36). The supportive inputs from these two partners primarily focused on improving the performance and capacity of health services, including collaborating with the MOHFW to ensure the availability of antibiotics at study area health centers and supporting training and supervision of providers. Project partners also worked with government frontline workers to promote awareness and community engagement with the public sector healthcare system. Beyond ensuring availability of oral amoxicillin at the health centers and training of providers in the guidelines, implementation support did not include activities with caregivers to promote adherence to the simplified antibiotic regimen.

Our study employed a mixed methods approach to data collection following a convergent parallel design where quantitative and qualitative data are collect concurrently (37). Data collectors visited the 19 UH&FWCs weekly to abstract data from facility records of young infants that sought services from October 2015-August 2016. Our study team aimed to follow-up all young infants (0-59 days) classified as infection at study area health centers to assess compliance with referral, adherence to outpatient treatment, and treatment outcomes. Follow-up by the study team took place between days 9 and 15 of treatment to not interfere with government follow-up

visits on days 4 and 8. Caregivers of young infants that provided verbal consent were enrolled in the study. The study team administered a questionnaire to assess counseling and follow-up by the provider, frequency and total number of antibiotic doses provided, barriers to therapy, and examined caregivers' decision-making and confidence to give medicine to their infant. The questions on adherence to medicines administered within the home were adapted from the Medical Adherence Questionnaire (MAQ), which is a scale validated in low-literacy populations to identify barriers to treatment adherence (38).

In-depth interviews with caregivers were conducted in both study areas to explore barriers and facilitators to adherence. Caregivers were purposively selected based on their infant's categorization of infection. We conducted in-depth interviews with caregivers of infants for each category of PSBI. However, we prioritized reaching a point of saturation for the clinical severe infection cases because these infants receive referral to the hospital and are eligible for simplified antibiotic treatment, including two gentamicin injections, when referral is not feasible for families. The goal of these interviews was to assess acceptability of the guidelines and the facilitators and barriers to providing oral amoxicillin from the perception of caregivers of young infants receiving treatment according to the guidelines. In-depth interviews were used to assess the caregivers' understanding and experience with administering treatment (e.g., *how often did you give the medicine?).* We also asked questions to examine the caregivers' self-efficacy as it relates to their ability to give medicine to their infant as this has been shown to be a contributor to adherence (26).

All researchers following up the mothers in the community were Bangladeshi and conducted interviews in the local language (Sylheti in Sylhet, and Bangla in Chittagong). Interviews were recorded and transcribed into English by trained translators for analysis. Following the interviews, research assistants also participated in debriefing sessions led by the research officers utilizing a thematic framework. Notes from these debriefing sessions were also translated into English and included in our analysis.

Measurements

We defined adherence as caregivers' self-report of providing 10-14 doses of oral amoxicillin during the illness episode. This range was chosen based on WHO criteria for adherence and is consistent with other studies that define adherence as 80% compliance with the recommended doses (10, 19, 25). Mothers that reported giving their infants doses outside of this range were classified as one of two non-adherent groups: 1) Mothers providing fewer than 10 doses (i.e., underuse) or 2) Mothers that reported providing more than 14 doses (i.e., overuse).

We adapted the WHO adherence framework to outline relevant factors that may influence adherence to the oral amoxicillin regimen (Figure 1). *Social and economic factors* included mother's age, education, family size, religion, and mother's employment. We adapted WHO's dimension of *patient-related factors* to include factors related to both the mother and infant: *caregiver-related factors* (mother's role in decision-making for their child health and confidence to administer medicine to the baby) and *infant-related factors* (age and sex of the baby). The mother was considered to be involved in decision-making about child health if they reported being the primary decision-maker or is they shared responsibility of decision-making with their husband or another family member. We included the infant's infection classification as an *illness-related factor* to represent illness severity. *Provider-related factors* were reported by the caregiver and included counseling on continuing oral amoxicillin at home and receiving follow-up from the health center provider during the illness period. Medical counseling and reported follow-up from the provider were based on maternal responses in the follow-up questionnaire. *Therapy-related factors* included caregiver's report of any barriers to treatment.

Analysis

We calculated the frequency, proportion and corresponding 95% Confidence Interval (CI) for oral amoxicillin doses given at the health center and home of the infant. We used the conceptual model (Figure 1) to identify the independent variables with a potential effect on adherence. We examined unadjusted associations for all independent variables with the dependent

variable—fewer than ten doses, adherent (10-14 doses), or exceeded recommended doses—using Pearson's chi-squared test for independence. A multivariable multinomial regression model was fitted to estimate Relative Risk Ratios (RRR) and 95% CI adjusting for variables associated at $p<0.20$ in bivariate analysis. The variables for infant age and provider follow-up were also included in the multivariate model because of its importance to our conceptual model. We assessed collinearity for all independent variables in the final model and excluded any variables associated at $r >0.5$. No variables were excluded due to collinearity. Barriers to treatment were examined as both a combined variable (i.e., any barrier reported) and the distribution by adherence group was calculated for specific barriers. Quantitative data were analyzed using Stata version 14 (StataCorp LP).

For the qualitative analysis, we employed an integrated approach to development of the coding framework (39). The framework was developed using *a priori* codes derived from the interview guides and the research questions related to medication adherence. Emergent codes were added to the codebook as necessary to capture themes that were suggested in the data but not initially anticipated in the *a priori* codes. We coded transcripts using the computer software program Dedoose. This study employed analytical methods of continual analysis, coding, and memoing. Our team reviewed transcripts of respondents throughout the study period based on both inductive and deductive themes. We adapted the questionnaire to explore emergent themes (40). Ultimately, we developed a coding framework—including a priori and emergent codes—based on iterative review of the qualitative data, which was used for the final analysis. Each transcript was coded using this scheme and charting of the coded passages was used to facilitate interpretation of the data between two researchers.

5.3 Results

Of the 583 young infants classified as infection at the study area health centers, our team followed-up and enrolled 78.6% (N=458) of their caregivers during home visits (Figure 2). We

excluded young infants with critical illness and local bacterial infection (N=143) because they were not eligible for simplified treatment per the updated guidelines. We excluded caregivers that reported accepting referral to the higher-level facility (N=23) or changing treatment during the illness episode at the advice of a doctor (N=26). Questionnaires missing the number of doses provided at home were also excluded from the analysis (N=10). Ultimately, 229 young infants received oral amoxicillin from 17 health centers in Sylhet (N=7) and Lakshmipur (N=10) and were included in this analysis.

A total of 23 interviews were conducted with caregivers during the study period. For this analysis, we excluded caregivers that reported the baby was critically ill or the family accepted referral (N=4), and caregivers that reported the baby "had disease of the umbilicus" (e.g., local bacterial infection) (N=3) since these infants were not eligible for simplified antibiotic treatment according to the revised guidelines. A total of 16 caregivers were included in our analysis of barriers and facilitators to adherence.

Quantitative

Of these 229 infants, health center records indicated 99.1% (N=227/229) received the first dose of oral amoxicillin from the provider on the day of assessment. However, 93.3% (N=210/229) of caregivers reported their infant did not receive the first dose of oral amoxicillin at the facility (Table 1). 62.4% of caregivers reported (N=143/299) administering 10-14 doses of oral amoxicillin to the infant during the illness episode, which we classified as adhering to the regimen (Table 1). 14.8% (N=34/229) of caregivers reported giving the infant fewer than 10 doses at home and 22.7% (N=52/229) of caregivers reported exceeding 14 doses of oral amoxicillin. In bivariate analysis, adherence to the amoxicillin regimen was significantly different by study district, maternal education and for mothers that reported any barriers to providing treatment compared to mothers that reported no challenges ($p<0.05$) (Table 2).

In multivariate multinomial regression analyses, only provider-related and therapy-related factors were associated with non-adherence (Table 3). Only 20.5% (N=47/229) of

caregivers reported receiving follow-up from the provider after the initial day of treatment. Mothers that reported receiving follow-up from the provider during the illness period (e.g., day 4 follow-up) were less likely to provide fewer than ten doses than mothers who did not receive follow-up (RR: 0.19; 95% CI: 0.05 – 0.74). 30.6% (N=70/229) of caregivers reported experiencing challenges to providing treatment to the infant. Mothers that reported any barriers to giving oral antibiotics at home were more likely to give the baby fewer than ten doses (RR: 0.42; 95% CI: 0.22 – 0.78). No factors were found to be significantly associate with the caregivers reporting exceeding the recommended dosage for oral amoxicillin. When we examined the distribution of specific barriers reported by caregivers, we found mothers reporting the baby had a negative side effect after taking the medication was the only barrier that differed by adherence classification (Table 4).

Qualitative

During in-depth interviews, all mothers of sick infants reported feeling confident in their ability to administer oral amoxicillin to their infants at home. When asked if other family members were involved in helping to administer the medication, most caregivers reported relying on themselves to provide the medication according to the doctor's instructions. Occasionally, mothers said the baby's father or grandmother may help provide the medicine, especially if this family member accompanied the mom to the health center and heard the doctor's instructions.

Most mothers discussed receiving instructions from the provider on continuing medicine at home, but the extent and quality of counseling varied. Some mothers reported they received the oral amoxicillin already prepared by the provider, while others reported they were instructed to reconstitute the powder at home using water that had been boiled. When probed on the provider's instructions for giving the medication, caregivers reported a better understanding of the regimen when the provider had shown them how to measure the medicine in the dropper and demonstrated administering the first dose to the baby. As one mother recalled,

> *Doctor apa [SACMO] showed how feeding is to be done by the dropper, if one feeding was at 7 pm, the next feeding will be at 7 am of the next day* – Mother of sick infant

We found that mothers had better recall of the dosage amount when the provider marked the correct dosage line on the medicine dropper,

> *Drops was given. First mark to second mark of the drop were given 2 times daily. Doctor had written the ways of feeding and also told us verbally.* – Mother of sick young infant

Some mothers reported that they did not receive verbal counseling from the provider on administering the medicine, but rather instructions were only written on a prescription slip. Occasionally caregivers reported being instructed to give the full medicine bottle over a week's time. In these cases, the caregiver was not able to recall the amount they administered with each dose.

When probed on barriers to adhering to the treatment regimen, few mothers reported forgetting a dose, and most said that they did not have trouble remembering to give their infant the medications. When asked what she does to remember to administer the amoxicillin, one mother said with a smile, "We remember without any help. Our child's face reminds us. We always stay close to our children." When asked whether they had difficulty remembering the correct amount to give the child, the mothers indicated that they did not have an issue because they referred to the marked dropper, medicine bottle and/or prescription slip as a reminder. The most frequently reported reason for skipping a dose of treatment was if the infant vomited the medicine after ingesting it, which caused the mother to worry about the condition of the infant. Some mothers reported strategies for administering the dose to the baby; for example, feeding the medicine to the baby slowly from the dropper so that it was better tolerated. As one mother explained, "I need to feed slowly. She cannot eat when I feed quickly." Several mothers also reported consulting the provider if the baby vomited after medication was administered,

> *If the child vomits due to the medicine, then I stop giving it. Then I go to the doctor. The doctor tells me to give the medicine again after vomiting, about after 10 minutes.*
> – Mother sick young infant

> *If my child starts vomiting after giving medicine, then I will consult with the doctor who gave the medicine. I will ask if I should continue it or not. I will decide depending on what the doctor says.* –Mother sick young infant

For mothers that reported stopping the medicine before completing the full regimen, the most commonly reported reason was seeing improvement in the baby's condition. As one mother stated, "If the disease is gone, then I stop the medicine." When probed on what they do with any remaining medicine, few mothers said they saved the amoxicillin for another illness episode or another child. More often, mothers reported disposing any unused medicine because they had been instructed by providers to not reuse medicine that is unsealed or more than one week old.

5.5 Discussion

This study aimed to explore caregiver adherence to oral amoxicillin treatment for sick young infants receiving the simplified antibiotic therapy from outpatient health centers in Bangladesh. Few caregivers reported that their infants received any doses of oral amoxicillin at the health center, which conflicted with health center records. Nearly two-thirds of caregivers reported adhering to the correct range of oral amoxicillin doses at home. We adopted dimensions of the WHO framework for medication adherence to examine the association of factors that contributed to or hindered optimal adherence to the regimen (26). Our quantitative analysis indicates that mothers reporting any barriers to treatment were more likely to give their babies fewer than ten doses. However, receiving follow-up from the provider had a protective effect for underdosing. Qualitative data indicate caregivers are confident in their ability to give oral antibiotics to their babies and relied on the provider's instructions for determining the dosage amount and frequency. Caregivers reported better understanding of the home-based regimen when counseling included both verbal and written instructions—including marking the dosage line on the dropper—and the provider demonstrated administering the first dose to the infant. Caregivers identified the baby vomiting after ingesting the medicine as the primary reason for skipping doses, while their perception that the baby was no longer sick was often cited as the

reason for stopping treatment early. These findings suggest reinforcing the importance of follow-up and improving the quality of provider counseling—including demonstrating giving medicine to the baby, incorporating guidance on managing side-effects, and the importance of completing the full course of antibiotics—may improve caregiver adherence to the oral amoxicillin regimen.

According to the guidelines, providers should provide the first dose of oral amoxicillin on the day of assessment at the health center. When we compared data from health center records with the caregiver questionnaire, we found that 99.5% (N=209/210) of the infant records where caregivers reported receiving zero doses at the facility had the first oral amoxicillin dose recorded in the register. Discordance between these data sources suggest providers may be giving the caregivers the oral amoxicillin to administer at home without providing the first dose to the infant. Qualitative data supports this notion, as few caregivers reported that the provider demonstrated how to give medication to the infant. Furthermore, some caregivers stated they prepared the oral amoxicillin at home with boiling water. Previous analyses from this study identified few health centers had a source of clean water available (Applegate, Paper 1). In these facilities, providers may give the amoxicillin powder to be reconstituted by the caregiver at home. It is also possible that providers refrained from administering the first dose as a time-saving measure, or that caregivers in our study did not remember receiving the first dose of oral amoxicillin at the facility. Training and supervision sessions should reinforce to providers the importance of providing the first dose of oral amoxicillin to prevent delays in initiating treatment and demonstrate proper administration for caregivers. Future program efforts should explore this finding further to better understand potential barriers to preparing and administering the first dose in the health center.

A previous evaluation of IMCI practices in rural outpatient facilities in Bangladesh found less than 10% of caregivers of sick children were counseled on how to administer medications at home. In exit interviews, none of the caregivers could correctly describe how to administer oral antibiotics to the child at home (32). We found 87% of caregivers reported receiving counseling

on oral antibiotics, which caregivers reported contributed to a better understanding of the regimen. We also found caregivers that reported receiving follow-up from the provider were less likely to give the baby fewer than ten doses. Our findings are consistent with previous studies, which have identified communication between the provider and caregiver as a key factor for adherence to outpatient oral antibiotic regimens (21, 41). However, the association of barriers with non-adherence and qualitative data suggest targeting supports to improve the quality of counseling may further bolster adherence. In interviews, mothers reported skipping doses most frequently due to the baby vomiting the medicine, and the most common reason for the mom stopping treatment early was when they believed the baby recovered. Both barriers should be addressed in counseling—at the facility and during follow-up—and indicated on the written instructions. Less than one-quarter of caregivers reported receiving follow-up from the provider after the day of assessment at the health center. Future program training and supervision sessions should reinforce that follow-up of infants receiving outpatient treatment is critical for the safety of the baby and promoting caregiver adherence to oral amoxicillin (9). Strategies to monitor for accountability and improve providers' compliance with fourth day follow-up should be explored and tested as the guidelines are scaled-up nationwide.

Successful implementation of the revised WHO guidelines will increase access to antibiotic treatment as well as antibiotic consumption. The WHO guidelines recognize that extensive use of antimicrobials increases the risk of antimicrobial resistance. Compared to current recommendations, the revised WHO guidelines are not expected to increase the risk of antibiotic resistance, but it is recommended that surveillance be increased to monitor resistance patterns (9, 10). Like many adherence studies, the barriers included in our study questionnaire primarily focused on reasons caregivers skipped doses or stopped treatment early. Our model did not yield significant associations to help us explain why more than 20% of caregivers reported exceeding the recommended number of doses. Qualitative data suggest lack of counseling on continuing medication or poor specificity of instructions by providers may contribute to an excess use of

antibiotics. For example, some caregivers reported being instructed to give the full medicine bottle in a week but were not able to recall the amount per dose, which may have resulted in caregivers exceeding the optimal number of doses to finish the bottle. Future studies examining caregiver knowledge of rational antibiotic use are important for identifying drivers of overuse and ensuring access to antibiotics without excess usage (15, 16).

Surprisingly, we did not identify associations between caregiver-related factors and adherence. We explored caregiver self-efficacy to provide medication to the infant in both the questionnaire and interview guides but found little variation in caregivers' reported confidence to administer medication to the baby. Caregivers frequently reported confidence to administer antibiotics and relied on themselves to make decisions about continuing treatment or following-up with the doctor with questions. In this setting, antibiotic use for young children is common due to both a high number of illness episodes and widespread availability of over-the-counter antibiotics (22, 42, 43). Therefore, it is likely caregivers in our study have previous experience with giving antibiotics to infants and children, which may bolster their confidence. We also did not identify associations between adherence and infant or illness-related factors—such as age and infection classification. Additional research on caregiver adherence to oral antibiotic regimens for simplified antibiotic treatment in newborns is needed to explore predictors of adherence and contribute to an appropriate conceptual model.

One critical limitation of our study is that we were only able to follow-up 78.6% (N=458/583) of caregivers and infants in the community. Thus, we were not able to assess adherence for those caregivers and infants that were lost to follow-up, which may have differed significantly from our study population. Our outcome measure—caregiver's self-report of number of doses given to the infant—is a subjective measure of adherence and vulnerable to reactive effects and recall bias (26, 27, 37). Reactive effects may be a threat due to respondents' social desirability to respond favorably about adhering to treatment especially if they knowingly stopped administering treatment against recommendations. In attempt to control for this threat

and capture an objective measure of adherence, we asked to see the medication bottle and prescription slip prior to asking questions about dosage. However, many caregivers did not have the medicine bottle available at the time of the interview and the details of the prescription slip were not recorded by data collectors. As a result, caregivers' self-reported adherence to the regimen may be over- or underestimated compared to an objective measure of adherence (44).

Our study suggests healthcare providers are instrumental for promoting caregivers' adherence to ambulatory oral amoxicillin treatment for sick young infants. Promoting provider adherence to the guidelines, including follow-up with the caregiver during the illness episode, may reduce undertreatment of sick infants. Caregivers indicated that they rely on the providers' instructions for continuing medicine and will consult the provider when the baby experiences a side-effect to the medicine, such as vomiting. Efforts should be made to improve the quality of counseling and integrate messages on completing the full course and how to proceed when the baby has a negative reaction to the medicine. Future research is needed to explore drivers of caregivers' exceeding the recommended number of doses in this context.

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5.7 Tables for Paper 3

Table 1. Distribution of oral amoxicillin doses provided to the infant for the illness episode

Location	Doses Administered n (%) N=229	95% CI
Doses given at the facility		
Zero	210 (91.7%)	87.3% – 94.9%
One	11 (4.8%)	2.4% – 8.4%
Two	1 (0.4%)	0.01% – 2.4%
Don't know/Can't remember	7 (3.0%)	1.2% – 6.2%
Doses given at home		
<10	34 (14.8%)	10.5% – 20.1%
10-14	143 (62.4%)	55.8% – 68.7%
>14	52 (22.7%)	17.4% – 28.7%

Table 2: Bivariate analysis of variables with adherence

Characteristics	Total n (%) (N=229)	Adherent (10-14 doses) (N=143)	Underuse (< 10 doses) (N=34)	Overuse (>14 doses) (N=52)	P-value
Social and Economic Factors					
Study District					
Sylhet	50 (21.8%)	33 (66.0%)	13 (26.0%)	4 (8.0%)	0.003*
Lakshmipur	179 (78.17)	110 (61.5%)	21 (11.7%)	48 (26.8%)	
Maternal Age					
<20 years	47 (20.5%)	29 (61.7%)	2 (4.3%)	16 (34.0%)	0.067
20-29 years	126 (55.0%)	76 (60.3%)	23 (18.3%)	27 (21.4%)	
=>30 years	56 (24.5%)	38 (67.9%)	9 (16.1%)	9 (16.1%)	
Maternal Education					
No education	14 (6.1%)	9 (64.3%)	4 (28.6%)	1 (7.1%)	0.006*
1-5 years (Primary)	41 (17.9%)	30 (73.2%)	9 (22.0%)	2 (9.8%)	
=>6 years (Secondary & above)	174 (76.0%)	104 (59.8%)	21 (12.1%)	49 (28.2%)	
Religion					
Islam	225 (98.3%)	142 (99.3%)	32 (14.2%)	51 (22.7%)	0.116
Others	4 (1.8%)	1 (25.0%)	2 (50.0%)	1 (25.0%)	
Family size					
1-4	36 (15.7%)	17 (47.2%)	7 (19.4%)	12 (33.3%)	0.361
5-6	85 (37.1%)	51 (60.0%)	13 (15.3%)	21 (24.7%)	
7-8	69 (30.1%)	47 (68.1%)	10 (14.5%)	12 (17.4%)	
≥ 9	39 (17.0%)	28 (71.8%)	4 (10.3%)	7 (18.0%)	
Mother works					
Yes	39 (17.0%)	24 (61.5%)	6 (15.4%)	9 (23.1%)	0.991
No	190 (80.9%)	119 (62.6%)	28 (14.7%)	43 (22.6%)	
Caregiver-related factors					
Mother included in decision-making about child health					
Yes	177 (77.3%)	115 (65.0%)	28 (15.8%)	34 (19.2%)	0.064
No	52 (22.7%)	28 (53.9%)	6 (11.5%)	18 (34.6%)	
Mother can take child to health center alone					
Yes	110 (48.0%)	71 (64.6%)	21 (17.7%)	26 (23.6%)	0.463
No	119 (52.0%)	72 (60.5%)	13 (11.8%)	26 (21.9%)	
Caregiver confidence in ability to administer medicine					

Characteristics	Total n (%) (N=229)	Adherent (10-14 doses) (N=143)	Underuse (< 10 doses) (N=34)	Overuse (>14 doses) (N=52)	P-value
Not confident	2 (0.9%)	1 (33.3%)	2 (66.7%)	0 (0%)	
Somewhat confident	37 (16.2%)	22 (59.5%)	7 (18.9%)	8 (21.6%)	0.116
Very confident	189 (82.9%)	120 (63.5%)	25 (13.2%)	44 (23.3%)	
Infant-related factors					
Age of infant					
<7 days	16 (7.0%)	9 (56.3%)	4 (25.0%)	3 (18.8%)	
7-28 days	75 (32.8%)	49 (65.3%)	13 (17.3%)	13 (17.3%)	0.407
29-59 days	138 (60.3%)	85 (61.6%)	17 (12.3%)	36 (26.1%)	
Sex					
Male	133 (58.1%)	83 (58.0%)	21 (15.8%)	29 (58.1%)	0.859
Female	96 (41.9%)	60 (42.0%)	13 (13.5%)	23 (41.9%)	
Illness-related factors					
Illness classification					
CSI	60 (26.2%)	33 (55.0%)	14 (23.3%)	13 (21.7%)	0.095
IFB	169 (73.8%)	110 (65.1%)	20 (11.8%)	39 (23.1%)	
Healthcare provider-related factors					
Counseling on continuing medication at home					
Yes	201 (87.8%)	130 (64.7%)	28 (13.4%)	43 (21.4%)	0.174
No	28 (12.2%)	13 (46.4%)	6 (21.4%)	9 (32.1%)	
Received follow-up from provider					
Yes	47 (20.5%)	34 (72.3%)	4 (8.5%)	9 (19.2%)	0.240
No	182 (79.5%)	109 (59.9%)	30 (16.5%)	43 (23.6%)	
Therapy-related factors					
Caregiver reported any barriers to treatment					
Yes	70 (30.6%)	34 (48.6%)	18 (25.7%)	18 (25.7%)	0.003*
No	159 (69.4%)	109 (68.6%)	16 (10.1%)	34 (21.4%)	

***Indicates significant values at p<0.05**

Table 3. Multinomial logistic regression of factors associated with caregiver-reported dosage not meeting or exceeding the recommended oral amoxicillin regimen for young infants receiving simplified antibiotic treatment

Characteristics (N=229)	Relative Risk Ratios (RRR) (95% CI)	
	Underuse (<10 doses) vs. Adherent (10-14 doses)	Overuse (>14 doses) vs. Adherent (10-14 doses)
Social and economic factors		
Study District		
Sylhet	ref	ref
Lakshmipur	0.49 (0.15 – 1.52)	2.86 (0.74-11.05)
Maternal Age		
<20 years	ref	
20-29 years	3.39 (0.70-16.50)	0.72 (0.32-1.62)
=>30 years	2.32 (0.41-13.12)	0.80 (0.28-2.27)
Religion		
Islam	0.35 (0.02 – 7.00)	0.49 (0.03-9.01)
Others	ref	ref
Maternal Education		
No education	ref	ref
1-5 years (Primary)	0.91 (0.19 – 4.39)	0.52 (0.04-7.16)
=>6 years (Secondary & above)	0.44 (0.08 – 2.23.40)	2.83 (0.29-27.35)
Caregiver-related factors		
Mother involved in decision-making about child health		
Yes	1.14 (0.38 – 3.41)	0.47 (0.22-1.03)
No	ref	ref
Caregiver confidence in ability to administer medicine		
Not confident	ref	ref
Somewhat confident	0.22 (0.02 – 3.14)	232993.9 (0)
Very confident	0.16 (0.01 – 2.00)	221220.3 (0)
Infant-related factors		
Age of infant		
<7 days	ref	ref
7-28 days	0.57 (0.11 – 3.08)	1.26 (0.23-6.75)
29-59 days	0.56 (0.12 – 2.70)	2.28 (0.48-10.91)

Characteristics (N=229)	Relative Risk Ratios (RRR) (95% CI)	
	Underuse (<10 doses) vs. Adherent (10-14 doses)	**Overuse (>14 doses) vs. Adherent (10-14 doses)**
Illness-related factors		
Illness classification		
Clinical severe infection	2.22 (0.79 – 6.17)	2.11 (0.83-5.39)
Isolated fast breathing	ref	ref
Healthcare provider-related factors		
Counseling on continuing medication at home		
Yes	0.44 (0.12 – 1.59)	0.37 (0.13-1.03)
No	ref	ref
Received follow-up from provider		
Yes	0.19 (0.05 – 0.74)*	1.29 (0.48-3.49)
No	ref	ref
Therapy-related characteristics		
Caregiver reported barriers to treatment		
Yes	4.14 (1.69 – 10.18)*	1.62 (0.77-3.42)
No	ref	ref

***Indicates significant values at p<0.05**

Table 4. Distribution of caregiver-reported barriers across adherence groups

Characteristic	Total (N=229) N (%)	Underuse (< 10 doses)	Adherent (10-14 doses)	Overuse (>14 doses)	P-value
Reported Barriers					
No barriers	159 (69.4%)	16 (10.1%)	109 (68.6%)	34 (21.4%)	0.003
Forgot to administer a dose	22 (9.6%)	4 (18.2%)	13 (59.1%)	5 (22.7%)	0.402
Inconvenience	4 (1.8%)	1 (25.0%)	1 (25.0%)	2 (50.0%)	0.324
Baby had a negative side effect	12 (5.24%)	9 (75.0%)	3 (25.0%)	0	< 0.001
Baby's condition improved	14 (6.1%)	4 (28.6%)	7 (50.0%)	3 (21.4%)	0.302
Other	18 (7.9%)	0	10 (55.6%)	8 (44.4%)	0.105

5.7 Figures for Paper 3

Figure 1. Conceptual framework for assessing adherence to outpatient oral amoxicillin regimen

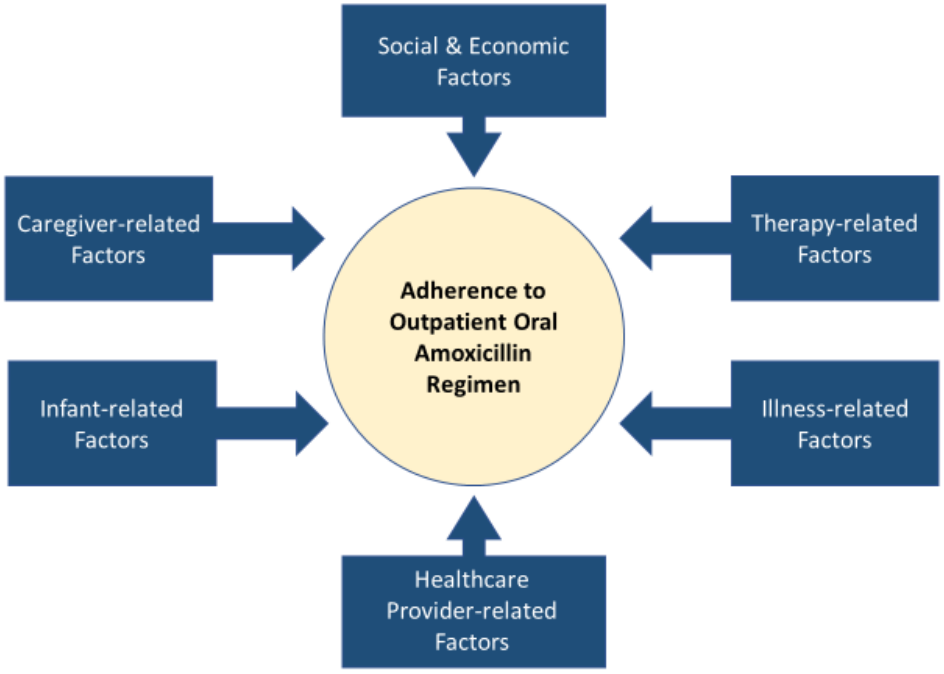
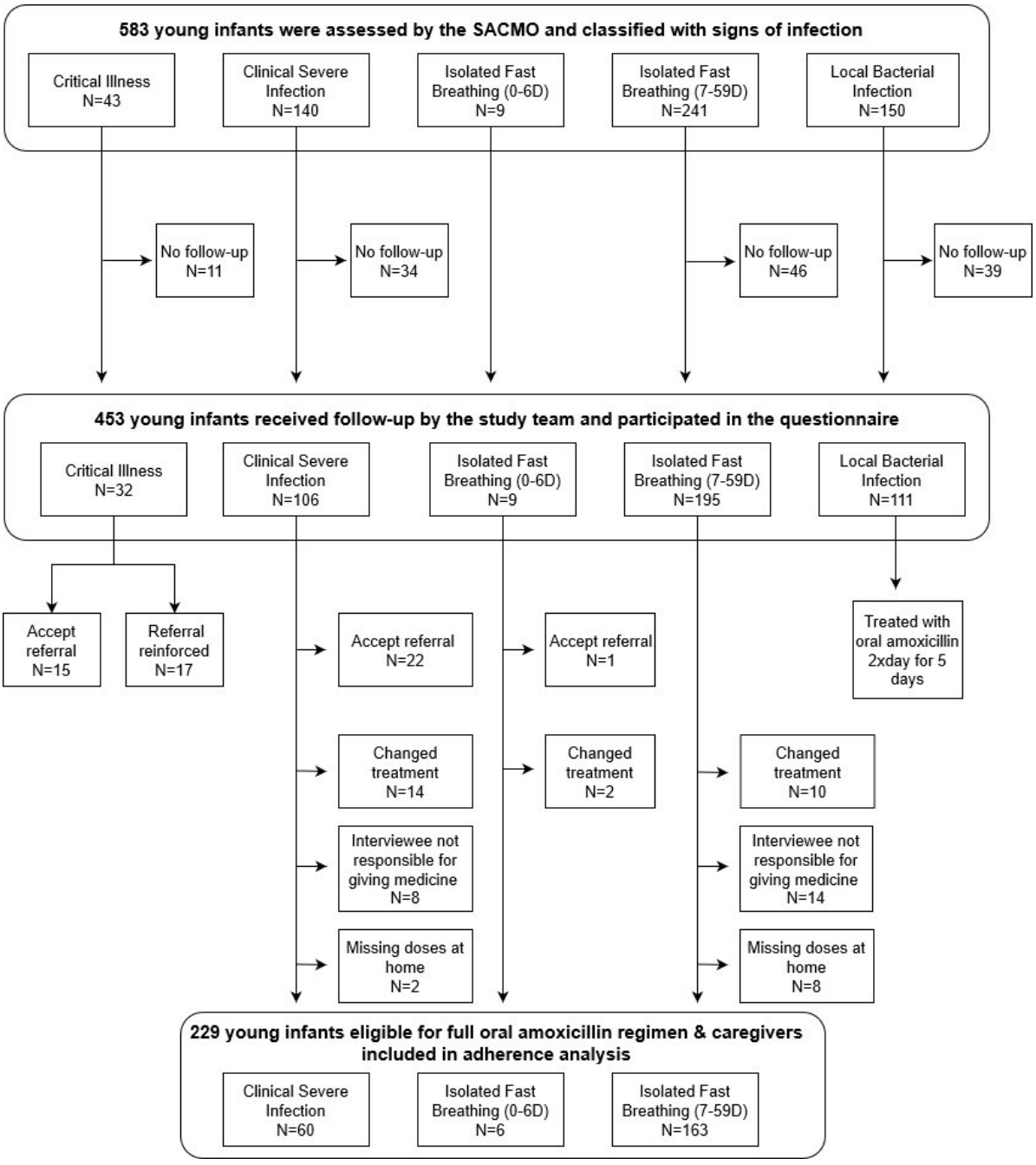


Figure 2. Flowchart of young infants included in caregiver adherence analysis



Chapter 6. Discussion

6.1 Summary of study findings

Increasing families' access to appropriate care and timely antibiotic treatment for newborn infections is critical to reduce neonatal mortality. WHO's guidelines for managing PSBI in young infants with simplified antibiotic treatment is an evidence-based intervention that will make it possible for families to access treatment for their sick infants when hospital referral is not feasible. Implementation of public health programs and policies, however, is known to be challenging—especially in resource-constrained settings where the need is often greatest. Mixed methods assessment of implementation research outcomes allowed for exploration of implementation fidelity and acceptability of the guidelines (Table 1). Findings described in this thesis will enable more effective problem-solving by policymakers and programs to strengthen implementation of Bangladesh's national guidelines and inform strategies for scale-up of the intervention nationwide.

Paper 1: Health facility readiness and provider performance

The aim of this paper was to assess facility readiness and provider performance on key components of the guidelines—classification and antibiotic treatment—over the study period. In the implementation research literature, the extent to which an intervention was implemented as intended in the original protocol is known as *fidelity* (1). Vacancies in the SACMO position limited the number of facilities included in this study and receiving implementation support for program rollout. At baseline, none of the included facilities had adequate supply of antibiotics of all functioning equipment required for guideline implementation, which were supplied by implementation partners during the study period.

Provider performance on the guidelines varied by facility and infection severity. Errors in classification and antibiotic dosage were highest at the beginning of the study period and

decreased over time. Interviews with providers suggest errors in early implementation may be due to providers learning new methods for assessment, classification, and treatment; and some providers' concerns about the efficacy of simplified antibiotic regimens. Strategies to monitor early performance and targeted supports are important for enhancing implementation fidelity.

Paper 2: Caregiver acceptability of guidelines

This study aimed to explore acceptability of the infection management guidelines from the perception of caregivers and providers. Few caregivers accepted referral to the sub-district hospital, suggesting low acceptability of this option for continued care and reinforcing the value of the simplified antibiotic treatment option. Barriers to referral feasibility included economic and household factors, and previous experiences with poor quality of care at the sub-district hospital. When referral was not accepted, providers and caregivers indicated high acceptability of simplified antibiotic treatment for infants receiving outpatient treatment, which they attributed to caregiver preference for providing oral antibiotics at home versus continued parenteral treatment at the hospital, reduced medical and travel costs, and less time away from their household and other children. Some providers reported developing local solutions—including engaging informal providers to provide the second gentamicin injection—to address organizational barriers and promote compliance with the simplified antibiotic regimen. Follow-up of young infants receiving simplified treatment is critical, but only about two-thirds of infants received fourth day follow-up. Some providers' reported deviations from the guidelines that shifted responsibility of follow-up to the caregiver, which may have contributed to lapses.

Caregivers' perception of trust and communication with providers were influential in caregiver acceptability of care. These findings suggest strengthening providers' interpersonal skills—including training on counseling that is culturally sensitive—and reinforcing the responsibility of the provider to initiate and continue follow-up could improve compliance and acceptability of the guidelines.

Paper 3: Caregiver adherence to oral amoxicillin regimen

The simplified antibiotic regimen includes a critical home-based treatment component—oral amoxicillin twice daily for seven days. The aim of this paper was to assess patterns and determinants of caregivers' adherence to outpatient oral amoxicillin treatment to contribute to our measure of implementation fidelity. Nearly two-thirds of mothers reported providing an acceptable dosage range to their infants. Caregivers had a better understanding of the regimen when the provider utilized multiple strategies for communicating the instructions—including verbal and written instructions, marking the dropper to reflect the dosage amount and demonstrating how to give the first dose.

Mothers that reported receiving follow-up from the provider during the illness period were less likely to provide too few doses; while mothers that reported any barriers to giving oral antibiotics were more likely to provide below the recommended dosage. Caregivers discussed skipping doses when the baby experienced side-effects to the medicine (e.g., vomiting), and indicated they would discontinue treatment if they believed the baby was no longer sick. Improving the quality of counseling to include messages on handling side-effects and reinforcing the need to complete the full course of antibiotics may improve caregiver adherence. Strategies are needed to improve provider adherence to the guidelines—including provision of the first dose and day 4 follow-up.

6.2 Implications for policy and practice

This study was designed to capture the implementation experience of the updated PSBI guidelines through systematic data collection in a real-world setting. The findings from this study will contribute to the global efforts of WHO to increase treatment access for families of young infants in low-resource settings that cannot accept hospital care, which has the potential to reduce infant deaths globally. Our primary objective, however, was to provide the Bangladesh MOHFW and implementing partners with findings to strengthen implementation and inform nationwide

scale-up of the guidelines within Bangladesh. Therefore, this section focuses on the study implications within this context, including recommendations for the MOHFW and our implementing partners in Bangladesh (Box 1).

Project inputs were required for ensuring health centers had functioning equipment and adequate supply of gentamicin and oral amoxicillin. Since the conclusion of our study, Bangladesh has incorporated the infection management guidelines into their current National Newborn Health Program as part of the 4th Health, Population and Nutrition Sector Program and secured the necessary budget for procurement of the essential drugs and equipment under this plan (2). While this policy provides the mechanism for procuring and supplying antibiotics to the targeted health centers, our findings suggest potential challenges to the structure of healthcare provision—including shortages of health workers and poor facility infrastructure—may adversely affect fidelity of implementation. For example, clean water is important for reconstituting the oral amoxicillin powder, but few health centers in our study area facilities had provision for clean water, which may serve as a barrier for providers giving babies the first dose of oral amoxicillin. Development partners should continue to monitor and advocate for facility strengthening as bottlenecks in supply chains and health worker vacancies threaten scale-up and sustainability of the program.

As providers gained practice with using new equipment, classifying infants according to the algorithm and calculating dosage, their adherence to the guidelines improved. Strategies to monitor early performance and targeted supports to underperforming facilities may accelerate this learning curve. Improving the quality of mentoring—including engaging providers in developing local solutions—may improve providers' ownership of the guidelines and help identify early barriers to implementation. For example, stakeholder meetings were important for identifying early challenges and informed subsequent supervision and refresher trainings.

Our findings also suggest strengthening providers' counseling skills, incorporating culturally sensitive messages, may improve both caregiver acceptability of the guidelines and

adherence to the oral amoxicillin regimen. For example, caregivers demonstrated a better understanding of the oral amoxicillin regimen when providers employed multiple strategies for continuing treatment at home—including verbal and written instructions, marking the amount on the dropper, and demonstrating the first dose. Additionally, incorporating messages on potential side-effects of oral amoxicillin (e.g., vomiting)—including directions on re-administering the dose—and the importance of completing the full course of antibiotics may improve adherence. Furthermore, strategies to monitor for accountability and improve providers' compliance with fourth day follow-up should be prioritized. In addition to ensuring the safety of the infant, caregivers reported greater acceptability of the guidelines and improved adherence to oral amoxicillin when they received follow-up from the provider.

Uncertainty around treatment outcomes, especially for referred cases, is a major barrier to monitoring the long-term effectiveness of the program. The guidelines recommend that providers follow-up with the caregiver, or hospital providers, to ensure families reach the referral facility; however, this follow-up is not recorded in the registers, so the health outcomes of these infants are not routinely tracked. Families that accept referral are more likely to have infants with serious illness and—in the current system—are more likely to be lost to follow-up. Systems for tracking referral cases need to be established and tested during rollout of the guidelines, and indicators for monitoring the care and outcomes of these cases should be integrated into routine systems. For PSBI cases receiving outpatient treatment, the day 8 follow-up visit is critical for assessing treatment outcomes. However, we found this visit was not regularly happening. Further investigation into improving functionality of these visits is needed as this strategy is scaled-up in Bangladesh.

6.3 Strengths and limitations

The major strength of this study is the use of both quantitative and qualitative approaches to provide a deeper understanding of the research questions than either method separately (3, 4).

The mixed methods design is well-suited to implementation research because it provides a way to understand multiple perspectives, different types of causal pathways, and multiple outcomes (1, 5). However, our study had several limitations including a short study period and lack of a comparison group. Our study period was limited to one-year, which was necessary based on the government's plans for scale-up. The lack of a comparison group and lack of randomization make the study more vulnerable to internal and external threats to validity. We aimed to improve internal validity by collecting data at multiple points in time. We extracted data on case management at all facilities implementing the guidelines in our study area on a weekly basis, administered the facility checklist prior to rollout and at two additional time points, and conducted interviews with all providers in our study area. Collecting both quantitative and qualitative data at multiple time points allowed us to assess trends in provider performance and identify changes in barriers and facilitators to implementation over the study period. However, we were unable to causally link implementation strategies to changes in practice outcomes due to lack of a comparison group (6).

Another limitation is that we do not have specific measures of quality of care at the study area health centers. We aimed to explore caregiver acceptability of the guidelines and their perceptions of the quality of public sector care based on a follow-up questionnaire and interviews. However, this study would have been strengthened by the direct observations of care. The estimated incidence of PSBI in young infants (95.4/1000) (7) in this setting, coupled with low care-seeking rates from the primary health facilities, led us to expect few infants would seek care at the study area health centers during the initial implementation period. Thus, direct observations of care were not feasible, and we were limited to analysis of facility records and qualitative interviews to assess compliance with the guidelines. There is variation among providers in how they record and report data, which was not controlled for in our data collection. Therefore, our data is subject to reporting bias and performance on care indicators should be interpreted judiciously. For example, we found discrepancies between the providers' registers and

caregivers' report for oral amoxicillin treatment, which suggests potential reporting bias among providers. However, it is also possible that some of these discrepancies are due to errors in caregiver recall. Future program efforts should review register completeness during supervision, or periodic program review, to monitor for accountability and address challenges associated with incomplete registers in a timely manner.

We were unable to follow-up more that 20% of the caregivers to assess patterns and determinants of antibiotic adherence. This is a major limitation of our study because adherence for those caregivers may have differed significantly from the caregivers that participated in the study questionnaire. Additionally, this limited our ability to explore agreement between provider and caregiver reports of care received for sick infants in our study area. Our analysis of adherence was based on a caregiver report of the number of doses provided, which is a subjective measure of adherence. Reactive effects may be a threat due to respondents' social desirability to respond favorably about adhering to treatment especially if they knowingly stopped administering treatment against recommendations. In attempt to control for this threat and capture an objective measure of adherence, we asked to see the medication bottle and prescription slip prior to asking questions dosage. However, many caregivers did not have the medicine bottle available at the time of the interview and the details of the prescription slip were not recorded by data collectors. As a result, caregiver self-reported adherence to the regimen may be over- or underestimated compared to an objective measure of adherence (8).

Finally, the potential lack of generalizability of these study findings to other developing country settings is a limitation of this study. Although generalizability was not a primary goal for this study, it will be important to consider this when formulating conclusions for dissemination globally. Additionally, it will be important to compare our findings with those from the other WHO-coordinated implementation research sites to learn about other countries' experience implementing the guidelines and improve external validity.

6.4 Future research

Based on expected PSBI incidence for young infants in this context, we estimated that only 16.3% of the expected cases sought care from the study area health centers. Our findings indicate informal providers were the preferred first choice in care due to their ability to meet the caregivers' emotional and social needs, reliability in providing drugs, and accessibility. Low rates of utilization are a major threat to the sustainability of this intervention. Our findings suggest potential strategies for improving caregivers' trust in public sector providers, but further investigation is needed to assess care-seeking patterns and determinants in this population. Additionally, strategies for changing care-seeking behavior should be tested and tailored to fit the local context.

Referral to the hospital remains the first-line recommendation for PSBI cases (9). However, few caregivers accepted referral to the sub-district hospitals, suggesting low acceptability of this option. Caregivers indicated distrust in hospital doctors, inconsistent availability of medicines, and financial constraints as the primary barriers to referral feasibility. Our study did not include implementation support activities or data collection at the sub-district hospital (i.e., UHC)—the recommended referral facility. Thus, we do not have data from the referral facilities to assess referral compliance, quality of care provided, or treatment outcomes for families accepting referral. Given referral complexities identified in this study, we anticipate referral compliance to be lower than acceptance rates recorded in the union-level health center records. Future studies should include data collection at public sector referral facilities to better understand barriers to referral compliance, quality of care, and identify opportunities for strengthening management of newborn infections.

Providers and caregivers indicated high acceptability of simplified antibiotic treatment for infants receiving outpatient treatment. For infants with clinical severe infection receiving simplified antibiotic treatment, the second gentamicin injection is critical. Local solutions for

promoting compliance when the visit falls on a weekend or a day when the UH&FWC provider(s) are unavailable—including potential engagement with the private sector—need to be explored further in this context. Future studies are needed to examine the potential for engaging informal and formal private providers, including the potential for fostering public-private partnerships (PPP) in this context (10-12). Additionally, public sector providers' opinions around engaging with private providers as allies should be explored as this has previously been identified as a barrier to implementation of PPP (13).

Some providers indicated their preference to begin treatment of PSBI in young infants with more expensive, broader spectrum antibiotics, despite WHO recommendations to reserve these drugs for after first-line antibiotic treatment (e.g., gentamicin & amoxicillin) fails. Additionally, nearly one quarter of caregivers reported exceeding the recommended dosage of oral amoxicillin when providing treatment to their infants at home. These findings suggest potential misuse of antibiotics, by both providers and caregivers, which may contribute to increasing rates of antibiotic resistance in this setting. Promoting rational antibiotic use in Bangladesh is complicated by both the lack of access to quality care and an abundance of access to antibiotics from unregulated providers and pharmacies (14). Strategic planning to curb antibiotic resistance is necessary for preserving the effectiveness of existing first-line antibiotics, preventing rises in childhood morbidity and mortality due to bacterial resistance, and controlling the economic burden that antibiotic resistance poses to the health system (15, 16). Future research should examine drivers of antibiotic misuse in this setting, including providers' assessment of effectiveness of simplified antibiotic regimens, the influence of pharmaceutical companies and market demand on prescribing practices, and caregiver knowledge and perceptions of appropriate antibiotic use.

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6.6 Tables for Chapter 6

Table 1. Framework of implementation research outcomes and mixed methods findings by dissertation study objective

Implementation Research Study Objectives			**Mixed Methods Findings**
Outcome	**Definition**	**Research Questions**	
Fidelity	The extent to which the intervention was implemented as intended in the original protocol	Were health systems supports available to ensure providers could deliver the program as planned?	• Project inputs were required for ensuring health centers had functioning equipment and adequate supply of oral amoxicillin. As providers gained practice with using new equipment and calculating dosage, their adherence to the guidelines improved. • Provider adherence to the guidelines improved over the study period, largely due to improvements in correctly classifying signs of clinical severe infection and calculating dosage of oral amoxicillin. • Clinical supervision, mentoring and training sessions were valued by providers and may have accelerated improvements in implementation fidelity. Stakeholder meetings were important for identifying early challenges and informed subsequent supervision and refresher trainings.
		To what extent did providers adhere to the guidelines?	
		To what extent did caregivers adhere to the oral amoxicillin regimen?	• Patterns of non-adherence included caregivers giving too few and too many doses of oral amoxicillin. Caregivers demonstrated a better understanding of the oral amoxicillin regimen when providers employed multiple strategies for explaining the regimen—including verbal and written instructions, marking the amount on the dropper and demonstrating the first dose
		What are the determinants of non-adherence?	

			• Provider adherence to the guidelines—including demonstrating the first dose of oral amoxicillin and engaging in follow-up—were associated with improvements in caregiver adherence practices • Caregivers that reported barriers to treatment (e.g., baby vomiting the medicine) were more likely to provide too few doses of amoxicillin, which may be due to both skipping doses or stopping treatment early if they believed the baby was no longer sick
Acceptability	Perception among stakeholders that the intervention is agreeable or satisfactory	Where were there gaps in service delivery and care of PSBI cases?	• Few caregivers accepted referral to the sub-district hospitals, suggesting low acceptability of this option. Caregivers indicated distrust in hospital doctors, inconsistent availability of medicines, and financial constraints as the primary barriers to referral feasibility. • Referral cases are not currently tracked, so providers rarely knew the treatment outcome for these sick infants. Some providers reported facilitating referral by calling the UHC and following-up with the caregiver, which increased caregivers' satisfaction with care. • Providers and caregivers indicated high acceptability of simplified antibiotic treatment for infants receiving outpatient treatment, which they attributed to caregiver preference for providing oral antibiotics at home, reduced medical and travel costs, and less time away from their household and other children. • Few infants sought care from the study area health centers during early implementation, which may be due to caregiver preference for care from the private sector, including informal providers in their community.
		What was the uptake of the intervention by families in the community?	

Box 1. Recommendations for strengthening implementation of Bangladesh's infection management guidelines for young infants in rural primary health centers

- Practical training on recognizing and interpreting the signs of PSBI and calculating antibiotic dosage according to the baby's weight and dosage chart may improve provider performance on the guidelines. Training should also incorporate provider education on appropriate antibiotic use and the effectiveness of gentamicin and amoxicillin for treating newborns with community-acquired infections in this setting.

- Strategies to monitor early performance and targeted supports to underperforming facilities may accelerate provider adherence to the guidelines.

- Improving the quality of mentoring—including engaging providers in developing local solutions—may improve providers' ownership of the guidelines and aid in identifying early barriers to implementation.

- Training and supervision should emphasize the clinical and teaching value of providing the full course of antibiotics and administering the first dose of oral amoxicillin at the facility. Potential barriers to providers preparing and demonstrating the first dose—including availability of clean water in the facility—should be explored as the guidelines are rolled out to new areas.

- Counseling was considered important by providers and caregivers. Training and supervision should aim to strengthen provider counseling skills through:

    - Practicing case scenarios for different types of infection classification to cover counseling on pre-referral antibiotic treatment, hospital referral, the simplified regimen, and plans for follow-up
    - Emphasizing the need for providing verbal and written instructions for cases accepting referral and cases receiving the oral amoxicillin regimen
    - Encourage continued communication with the caregiver and ensure the caregiver has the provider's phone number
    - Encourage the provider to include other family members (e.g., the baby's father and grandmother) whenever possible

- Counseling modules should also incorporate culturally sensitive messages on:

    - Clinical importance of the gentamicin injections and address caregiver fears about medicines weakening the baby
    - Potential side-effects to oral amoxicillin (e.g., vomiting) and directions on re-administering the dose
    - Importance of completing the full course of oral amoxicillin even if the baby is no longer symptomatic

- Referral to the hospital remains the first-line recommendation for PSBI cases. Referral linkages between the UH&FWC and UHC should be strengthened and indicators for tracking referral cases are needed in HMIS. In the interim, UH&FWC providers should initiate contact with UHC providers to alert them to a new case and follow-up with caregivers to ensure they reached the facility.

Box 1. Recommendations for strengthening implementation of Bangladesh's infection management guidelines for young infants in rural primary health centers

- For infants with clinical severe infection receiving simplified antibiotic treatment, the second gentamicin injection is critical. Local solutions for promoting compliance when the visit falls on a weekend or the UH&FWC provider(s) are unavailable—including potential engagement with the private sector—need to be explored further.

- Strategies to monitor for accountability and improve providers' compliance with fourth day follow-up should be prioritized. In addition to ensuring the safety of the infant, caregivers reported greater acceptability of the guidelines and improved adherence to oral amoxicillin when they received follow-up from the provider.

- Day 8 follow-up did not happen regularly in early implementation. Barriers to this visit by the Family Planning Inspectors (FPI) need to be explored further to develop strategies for improving the functionality of this visit.

Appendices

Appendix 1. Guideline-specific register for recording case management

রেজি: নম্বর (বাৎসরিক ক্রমিক/সন) ও তারিখ (Reg NO. Year & Date)	সেবা গ্রহীতার পরিচিতি (Information of care taker)	লিঙ্গ (Sex)	ঈরীক্ষা (Examination)	লক্ষণ (Sign)	সংক্রমণের শ্রেণীবিভাগ (Classification)	চিকিৎসা ব্যবস্থাপনা (Management)	ফলোআপ (Follow up)	মন্তব্য (Comment)
১	২		৪	৫	৬	৭	৮	৮
	নাম : (Name) **বয়স** : (Age) **মায়ের নাম:** (Mother's name) **পিতার নাম** :(Father's name) **ঠিকানা** (Address) ☐ **বাড়ি বা বাড়ি প্রধানের নাম/হোল্ডিং নম্বর:** (Name of house or house owner/ holding no.) ☐ **গ্রাম :** (Village) ☐ **ইউনিয়ন:** (Union) ☐ **উপজেলা :** (Upazila) ☐ **জেলা:** (District) ☐ **মোবাইল নম্বর :** (Mobile no)	☐ ছেলে (Male) ☐ মেয়ে (Female)	তাপমাত্রা (° ফা): {Temperature (°F)} ..... ওজন (গ্রাম): {Weight (gm)}..... শ্বাস (মিনিটে কতবার): (Respiratory rate)..... জন্ডিস: (jaundice)	☐ অচেতন/ ঝিমুনী (Unconcious/ Drowsy) ☐ খিঁচুনী অথবা খিচুনীর ইতিহাস আছে (Convulsion or history of convulsion) ☐ একদম খেতে না পারা (Unable to feed) ☐ অনবরত বমি (আধাঘন্টার মধ্যে খাওয়ানোর সময় ৩ বার বমি) (Persistent vomiting) ☐ মাথার তালু স্ফীত হওয়া (Bulging Fontanelle) ☐ শিশুর শরীরের বিশেষ অংশ নীল বর্ণ ধারণ (Central Cyanosis) ☐ জন্ম ওজন ১৫০০ গ্রামের কম (Birth Weight <1500 grams)	☐ সংকটাপন্ন অসুস্থতা (Critical Illness)	প্রথম ডোজ প্রদান ও রেফার (Administrate 1st dose and refer) ☐ ইনজেকশন জেন্টামাইসিন (Inj. Gentamycin) : __ পরিমান (amount) ☐ এ্যামোক্সিলিন ড্রপ (Oral Amoxicillin drop) : __ পরিমান(amount) রেফার: (Reffer) কেন্দ্রের নাম: (Name of referral centre) সময় :(Time)		
				☐ বুকের নীচের অংশ মারাত্মক ভাবে ডেবে যাওয়া (Severe chest in-drawing) ☐ নিম্ন তাপমাত্রা (৩৫.৫° সে. বা ৯৫.৯°ফা. এর কম) {Hypothermia (<95.90F or 35.50C)} ☐ উচ্চ তাপমাত্রা বা জ্বর (৩৭.৫° সে. বা ৯৯.৫° ফা. এর বেশি) {Raised temperature (>99.50F or 37.50C)} ☐ মায়ের দুধ খেতে না পারা বা না চোষা (Not feeding well) ☐ নেতিয়ে পড়া বা স্বাভাবিকের চেয়ে কম নড়াচড়া করা (Less movement than normal)	☐ খুব মারাত্মক অসুস্থতা (Clinical Severe Illness)	প্রথম ডোজ প্রদান ও রেফার (Administrate 1st dose and refer) ☐ ইনজেকশন জেন্টামাইসিন : (Inj. Gentamycin) : __ পরিমান (amount) ☐ এ্যামোক্সিলিন ড্রপ : (Oral Amoxicillin drop): __ পরিমান (amount) **রেফার:** (Reffer) **(কেন্দ্রের নাম):** (Name of referral centre) সময় : (Time) ☐ রেফার সম্মত (Agreed to reffer) ☐ রেফার সম্মত নয় (If referral failure) (যদি পরিবার রোগীকে রেফার করতে না চায়) **পরামর্শ** (Advice) ☐ ইনজেকশন জেন্টামাইসিন: (Inj. Gentamycin) __পরিমান দিনে ১ বার মোট ২ দিন: {(__ amount) once daily for 2 days)} ☐ এ্যামোক্সিলিন ড্রপ: (Oral Amoxicillin drop) __ পরিমান (amount) দিনে ২ বার মোট ৭ দিন (Twice daily for 7 days)	**দ্বিতীয় দিনের ফলোআপ ও চিকিৎসা প্রদান** (Day 2- Follow up and Treatment) ☐ জেন্টামাইসিন এর দ্বিতীয় ডোজ প্রদান : __ (2nd dose of Inj. Gentamycin): __ পরিমান (dose) (এ্যামোক্সিলিন ড্রপ: ফলোআপ) {Oral Amoxicillin drop (Follow up)} **চতুর্থ দিন ফলোআপ** (Day 4- Follow up) ☐ করা হয়েছে (done) ☐ করা হয়নি (not done) ☐ সময়: (Time) **শারীরিক অবস্থাঃ** (Physical condition) ☐ উন্নতি হয়েছে (Improved) ☐ অপরিবর্তিত (not improved) ☐ অন্য লক্ষণ দেখা দিয়েছে (Other sign developed)	
				☐ দ্রুত শ্বাস (মিনিটে ৬০ বা তার বেশী) {Fast Breathing (Respiratory rate 60/min or more)}	☐ শুধুমাত্র দ্রুত শ্বাস (Fast Breathing as a Single Sign of Illness)	০-৬ দিনের শিশু (Newborn of 0-6 days) **চিকিৎসা** (Treatment) ☐ এ্যামোক্সিলিন ড্রপ **প্রদান ও রেফার** (Administration of Oral Amoxicillin drop and reffer) রেফার: (Reffer) কেন্দ্রের নাম: (Name of referral centre)	**চতুর্থ দিন ফলোআপ** (Day 4- Follow up) ☐ করা হয়েছে (done) ☐ করা হয়নি (not done) ☐ সময়: (Time) **শারীরিক অবস্থাঃ** (Physical condition) ☐ উন্নতি হয়েছে (Improved)	

						☐ রেফার সম্মত নয় (যদি পরিবার রোগীকে রেফার করতে না চায়) (If referral failure) পরামর্শ (Advice) ☐ এ্যামোক্সিলিন ড্রপ: (Oral Amoxicillin drop) ___ পরিমান (amount) দিনে ২ বার মোট ৭ দিন (Twice daily for 7 days) ৭-২৮ দিনের শিশু (Newborn aged 7-28 days) ☐ চিকিৎসা ও পরামর্শ (Treatment and advice) ☐ এ্যামোক্সিলিন ড্রপ : (Oral Amoxicillin drop) ___ পরিমান (amount) দিনে ২ বার মোট ৭ দিন (Twice daily for 7 days)	☐ অপরিবর্তিত (not improved) ☐ অন্য লক্ষণ দেখা দিয়েছে (Other sign developed)	
				☐ নাভীর চারপাশে লাল বা নাভী থেকে পুঁজ পড়া (Umbilicus redness or draining pus from umbilicus) ☐ ত্বকে পুঁজবটি (Pastules)	☐ স্থানীয় সীমিত সংক্রমণ (Local Bacterial Infection)	☐ চিকিৎসা ও পরামর্শ (Treatment and advice) ☐ এ্যামোক্সিলিন ড্রপ : (Oral Amoxicillin drop)		
				☐ অন্যান্য (নির্দিষ্ট করে লিখুন): Others (please specify)				

Appendix 2. Dosage chart

Antibiotic dosage for sepsis management of infant aged 0-59 days at Union health and family welfare center

Child Weight (kg)	Gentamycin dosage: 40 mg/ml (Intramuscular injection)			Amoxicillin dosage: 100 mg/ml (Oral)	
	Each dosage(ml)	Each dosage(mg)	Each dosage (Unit of Insulin Syringe)	Each dosage(mg)	Each dosage(ml)
1.50 < 1.75	0.15	6	15	80	0.8
1.75 < 2.0	0.17	6.8	17	90	0.9
2.0 < 2.5	0.2	8	20	110	1.1
2.5 < 3.0	0.35	14	35	140	1.4
3.0 < 3.5	0.45	18	45	160	1.6
3.5 < 4.0	0.5	20	50	190	1.9
4.0 < 4.5	0.55	22	55	210	2.1
4.5 < 5.0	0.6	24	60	240	2.4
5.0 < 5.5	0.7	28	70	260	2.6
5.5 < 6.0	0.75	30	75	290	2.9
6.0 < 6.5	0.8	32	80	310	3.1
Gentamycin Injection: This injection should be administered intramuscularly. Dosage: 5.0-7.5 mg/kg body weight once daily for total 2 days. Each 2 ml injection contains 80 mg gentamycin; i.e. each ml contains 40 mg gentamycin. Use insulin syringe to administer injection gentamycin for children.					
Amoxicillin Drop: Oral administration in children. Dosage: 50 mg /kg body weight in every 12 hours (twice daily) for 7 days. Each 1.25 ml contains 125 mg of amoxicillin. **Method of preparing drop:** First, shake the bottle properly to loosen all powder. Mix 10 ml (2 measuring spoon full) boiled cold water with powder into the bottle and shake the bottle well until all powder mixed properly.					

Appendix 3. Caregiver interview guide

In Depth Interview (IDI) Guide:
Caregivers of Cases

IRB No.: 6607
PI: Abdullah Baqui
PI Version: 2; Date: 28 March 2016

General instructions: Interviewers, please read the following opening script (Part B) to the respondent and then proceed with asking him/her the questions listed in Part C. Some questions have specific probes, but please feel free to probe on additional points of interest to guide the discussion as needed.

1. IDI Code:			**2. Interviewer Code:**		
3. Date:		**4. Start Time:**		**5. End time:**	
6. Location:			**7. Relationship of participant to infant:***(ex: Mother, Aunt, Grandmother)*		
8. Description of Setting (Surroundings, general atmosphere, weather, observations before starting IDI)					

Part B: Opening script

Opening script—Individual interview with Caregivers of Young Infant Infection Cases: Thank you for agreeing to participate in our study. As previously mentioned, we are going to ask you some questions about your experience as a caregiver of a young infant that was recently treated for infection. Please respond to these questions as honestly and descriptively as possible. Your identity will be kept confidential so please feel comfortable sharing your stories. We will now begin!

Part C: Guiding Questions

Illness Episode:

1. What are the symptoms that you first observed in your child during the illness you reported?
2. When did you decide to seek care out of the home?
    - What was the reason for seeking care?
    - Who made the decision to seek care?
    - How long after you recognized the first symptoms was this decision made?

Care Seeking:

3. Where did you first seek care? (Probe: self-medication, relatives/neighbors, medicine salesman, village doctor, traditional healer, religious leader, other?)
4. How did you come to the decision to bring your infant to this particular provider (FWC or other type of providers)?
5. How distant is your home from this center? What are the implications, if any, of this distance on your care seeking of your young infant?

Care experience:

6. Describe your visit with the provider (Probe: Ask the following questions about each source of care, and repeat the series of questions until there is no other source of care)
    - How long did you have to wait to see the provider?
    - Who treated your infant while you were there?
    - What did this provider tell you about the baby's illness?
    - What was treatment was given to the baby?
    - Was any injection or medication given?
    - What was the cost to you, if any, for the visit and services provided?

7. Do you visit the private chamber of SACMOS from FWCs? If yes, why? If you have experience of getting your young infant treated in both public and private sector, did you notice any difference? (Probe: What were the differences? Why do you think they did it differently?)

Referral experience

8. Did they make a referral for you to see another provider or hospital?
9. ***If no referral was made:** Please describe the advice that the provider gave to you
    a. **Probe:** Please describe what happened next
10. ***If a referral was made**: Did you accept the referral?
    a. If yes: Describe the process of how you got to the next facility
        i. Transport?
        ii. Cost?
        iii. How long after visit did you go to facility?
        iv. What treatment was given?
    b. If no:
        i. Why was referral refused?
        ii. Describe what happened next (Visiting any other provider)

Day 2 Follow Up Visit

11. After your baby was diagnosed, were you asked to return to the facility on the following day?
    - If no, what follow-up advice were you given?
    - If yes, did you return for this follow-up visit?
        - If you did not return on the next day, then why did you not return for the follow-up visit?
        - If you did return on the next day, can you tell me what happened?
            - What time of day did you arrive? How long did you wait to be seen?
            - Who cared for your infant?
            - What care was provided? What was discussed?
            - What was the cost to you, if any, for the visit and services provided

Treatment Adherence

12. What did you do to treat the sick infant at home?
    - How many days did you treat the infant for?
    - How much medicine did you give each day?
    - How did you decide on that course of treatment?
        - [if treatment was for less than the recommended number of days]: did you decide to stop the treatment early? Why? [if answer is no, explain the

number of days that are generally recommended, and ask if they were aware that this was the recommendation]

- Did you discuss treatment with any other family or community members? If so, whom?
- Is there any medicine remaining? Why?
- Would you show me the medicine bottles? (if available)
  - *Interviewer note: Please make a note of how much medicine if leftover. If possible take a picture of the bottle

Caregiver's self-efficacy about administering medication

13. Who fed the medication to the infant?

14. How did you feel about your ability to administer the medications to your infant properly?
    - If any, what were your reservations about administering the medications to your infant?

15. If any, can you describe the challenges you faced related to administering the medications?
    - Probe: Timing of administering medication?
    - Probe: Cooperation of infant in receiving medication?

16. How did you know that administration of the medication was successful?
    - What helpful strategies were used to administer the medication to your infant?
    - How did you feel after the medication was successfully administered to your infant?

17. What mode of treatment do you prefer- giving medicine to baby at home or taking the medicine at hospital? (Probe: Explore if there is any preference of one mode over the other)
    - Which method of treatment do you prefer? Why?
    - What would make administering the medication to your baby a more positive experience?

At-home Follow Up Visit

18. Did you receive any follow-up visits at home from a health provider?
    - If yes, please describe these visits
      - Where did they occur?
      - Who was the provider that made the visit?
      - How many days after your first visit to the UH&FWC did the visit happen? How many visits did you receive?
      - What happened during the visit?
    - What did you like about these visits?
    - If anything what would you change about the visit if you had the option?
    - What other follow-up services did you receive? When did you receive these services?
      - Probe: Did you receive a phone call? Text message?
      - Please tell me who called you and what was discussed.
19. Can you hold the SACMO accountable if there is any issue regarding the treatment and follow up of your young infant? How?

Treatment Outcome

20. What was the treatment outcome for your baby?
    - Why do you think this was the outcome?
    - Are you satisfied with the care you received from FWCs? Explain.

Other issues

1. Do you want to add anything else which we might have missed? (Probe: any suggestions, off the record complaints, challenges against care seeking, anything else)

Appendix 4. Caregiver group discussion guide

Focus Group Discussion Guide:
FGD with Caregivers of Young Infants

IRB No.: 6607
PI: Abdullah Baqui
PI Version: 2; Date: 18 November 2015

General instructions: This guide provides the questions and topics that will be addressed in the FGD. The guiding questions are listed by subheadings related to program processes. Please adhere to the following instructions when facilitating this FGD:

1. Please begin by welcoming individuals as they arrive to the FGD and obtaining *consent*
2. Fill out **Part A: Background Information** after obtaining consent and before starting the FGD.
3. When it is time to begin, start the recorder, welcome participants as a group and read **Part B: Opening Script**
4. Proceed with **Part C: Guiding Questions** and facilitate the discussion
5. After the discussion concludes, thank the caregivers for their participation, stop the recorder, and dismiss the participants. Record the end time on the **Part A: Background Information** table

Part A: Background Information

1. FGD Code:		**2. Facilitator Code:**			
3. Date:		**4. Start Time:**		**5. End time:**	
6. Location:		**7. # Of participants:**			
8. Description of Setting (Surroundings, general atmosphere, weather, observations before starting FGD)					
8. **Caregiver Information**					
Name (Code)	Gender	Religion	Relationship to child (Mother, grandmother, etc)		

Part B: Opening Scripts

Opening script—Group interview: *Good morning/afternoon, I would like to thank you for giving the time to speak with us in this interview in which we would like to learn more from you about your recent experience seeking care for your sick infant. Firstly, let me introduce myself. I am [name] and my colleagues are [name] and [name]. We are a team of researchers engaged by Johns Hopkins University to conduct a study in collaboration with the Ministry of Health in order to help strengthen this program. As such there are no right or wrong answers because you are only expected to share your experiences. In addition to that, let me say that the information that we share in this group should be considered confidential.*

Each of you has been given a number that will be used to record your comments, so you will not be identified by name. Please do not share the opinions of others outside of this group. We should respect each others' opinions and give each other turns when speaking.

Please let's begin with everyone introducing themselves using their number.

Part C: Guiding Questions

Care seeking:

1. How do caregivers of infants in the community know when their baby is sick? What symptoms would they notice?
    - Probe: Anything else?
2. When do caregivers in the community generally decide to seek care out of the home?
    - Probe: Who usually makes the decision to seek care?
3. Where do people usually first seek care when their babies are sick?
    - Why is this the first choice provider?
    - Describe what happens when people go to this provider? ?
        - Probe: What kind of care is administered?
4. Do people ever seek care from more than one provider?
    - If yes, where? Describe the experience.
    - If yes, why do they see more than one provider?

Care at the union facility

5. What do caregivers in the community think about the FWCs/Union Level Health Facilities?
    - What do people like about the FWC?
    - What do people dislike about going to the FWC?
    - What generally happens when someone visits an FWC with their sick baby?
        - Probe: Who cares for them (nurse, doctor, SACMO)?
        - Probe: How long is the wait to be seen?
        - Probe: What care is usually given?
    - What level of satisfaction or dissatisfaction do people have in regard to the care they receive at the FWC?
6. What kinds of referrals, if any, does the FWC usually make?
    - Do people generally follow referrals made by the FWC to other providers?
    - Why? Why not?
7. What other services do the FWCs provide?
    - What follow-up services are made by the FWC, if any?

Treatment Adherence

8. Describe how caregivers in the community generally feel about administering medication to their infants
    - What, if any, are the concerns they might have about administering medication themselves?

9. How do they learn the directions for administering medication to their infants?
    - When would they stop administering medication to the infant?
    - Is there ever any leftover medication? What happens if there are leftovers?

Appendix 5. Provider interview guide

In Depth Interview (IDI) Guide:
Health Providers (SACMO)

IRB No.: 6607
PI: Abdullah Baqui
PI Version: 1; Date: 29 September 2015

General instructions: Interviewers, please read the following opening script (Part B) to the respondent and then proceed with asking him/her the questions listed in Part C. Some questions have specific probes, but please feel free to probe on additional points of interest to guide the discussion as needed.

Part A: Background Information

1. IDI Code:		**2. Interviewer Code:**			
3. Date:		**4. Start Time:**		**5. End time:**	
6. Location:		**7. FWC where SACMO works:**			
8. Description of Setting (Surroundings, general atmosphere, weather, observations before starting IDI)					

Part B: Opening Scripts

Opening script—Individual interview with SACMO:Thank you for agreeing to participate in our study. As previously mentioned, we are going to ask you some questions about your experience as a SACMO implementing the new guidelines for infection management in young infants. Please respond to these questions as honestly and descriptively as possible. Your identity will be kept confidential so please feel comfortable sharing your stories. We will now begin!

Part C: Guiding Questions
Training

2. Tell me about the training that you participated in on the new guidelines (Probe: content, timing, who implemented)
3. What do you think worked well in the training? What didn't work well?
4. What changes are needed in the training approach, if you think anything should be changed

Case management

5. Please describe the last young infant that you saw, and how you used the new guidelines when treating this infant.
6. What challenges do you encounter in implementing the new guidelines?
    - Assessing cases?
    - Referring cases?
    - Treating cases?
7. What are the families' reactions to the treatment guidelines (referral and/or home treatment)?
    - Can you tell me about a specific example of how they reacted that way?
8. If there are any, what challenges to implementing the new guidelines exist?
    - How should they be addressed?

Technical Materials

9. Please tell me about the technical materials that support you in the implementation of the new guidelines (probe: job aid, register, etc)
    - What do you think is useful about these materials?
10. What improvements or changes would you make to these materials to make them more helpful, if any? address

Supervision

11. Please tell me about the last time you received a supervision visit and what happened during the visit?
12. How would you describe the effectiveness of the supervision visit?
    - Probe: Did you find the supervision visit to be helpful? Please explain.
13. What were your expectations of the supervision visit?
    - How did the supervision visit meet your expectations?
      What do you wish happened during the supervision visit that did not happen? Please explain.

Monitoring

14. What is the process for completing reports on the implementation of the new guidelines?
    - What is your opinion about the reporting format? (Probe: What are the good things? Things that need improvement?)
    - What changes would you like to see to the report, if any? (Probe: Format, frequency, content)
15. Please describe the feedback you have received on your reports if you have received any.

Supply chain

16. How are the UH&FWCs supplied with drugs for the new guidelines? (Probe: How does this compare to other drugs supplied to UH&FWC?)
17. What has been the status of the drug supply? Have there been any issues? (Probe: any stock outs?) What are the reasons?
18. What changes do you think should be made to the drug supply systems, if any?

Community mobilization

19. How are community mobilization events organized and implemented. Who attends?
20. What concerns came up in community mobilization events? How were these addressed?
21. What successes and challenges have you witnessed in this community mobilization approach? How would you improve the challenges faced?

Appendix 6. Provider group discussion guide

Focus Group Discussion Guide:
SACMO

IRB No.: 6607
PI: Abdullah Baqui
PI Version: 1; Date: 11 November 2015

General instructions: This guide provides the questions and topics that will be addressed in the FGD. The guiding questions are listed by subheadings ‡‡related to program processes. Please adhere to the following instructions when facilitating this FGD:

1. Please begin by welcoming individuals as they arrive to the FGD and obtaining *consent*
2. Fill out **Part A: Background Information** after obtaining consent and before starting the FGD.
3. When it is time to begin, start the recorder, welcome participants as a group and read **Part B: Opening Script**
4. Proceed with **Part C: Guiding Questions** and facilitate the discussion
5. After the discussion concludes, thank the SACMOs for their participation, stop the recorder, and dismiss the participants. Record the end time on the **Part A: Background Information** table

Part A: Background Information

1. FGD Code:		**2. Facilitator Code:**			
3. Date:		**4. Start Time:**		**5. End time:**	
6. Location:		**7. # Of participants:**			
8. Description of Setting (Surroundings, general atmosphere, weather, observations before starting FGD)					
8. **SACMO Information**					
Name (Code)	Gender	Religion	Years Working as a SACMO	Years Working Here	Do they belong to this area (union/upazila?)

Part B:

Opening Script
Good morning/afternoon, Thank you for taking the time to join this FGD in which we hope to learn more about the new guidelines for managing infections in young infants. I am [name] and my colleagues are [name] and [name]. We are a team of researchers engaged by Johns Hopkins University to conduct a study in collaboration with the MOH in order to help strengthen this program. Our main focus is to hear SACMO opinions about how the guidelines are working and how the program is supported.

In the discussion we will be interested to hear your experiences with the implementing the new guidelines for management of infections in young infants. As such there are no right or wrong answers because you are only expected to share your experiences. This

should not be viewed as a job evaluation exercise but rather a contribution to help strengthen the program. The information that you share with us will be combined with the opinions we receive from other participants, and your name will not be reported. The information that we share in this group should be considered confidential. Each of you has been given a number that will be used to record your comments, so you will not be identified by name. Please do not share the opinions of others outside of this group. We should respect each others' opinions and give each other turns when speaking. Please let's begin with everyone introducing themselves using their number, and telling the group how long you have been working in your position, and what you did prior to that.

Part C: Guiding Questions

Training

1. How do you and your SACMO colleagues generally feel about the training they received on the new guidelines?

Case management

2. What are the benefits that you and your colleagues see to using these new treatment guidelines?
3. What are the challenges when using these new guidelines when managing cases? How can these be addressed?
4. What are the families' reactions to the treatment guidelines (referral and/or home treatment)?

Technical Materials

5. Please share your opinion of the technical materials that support you in the implementation of the new guidelines (probe: job aid, register, etc.)

Managing infants with infection in private practice vs. public practice

6. Do you manage young infants with signs of infection differently in your private practice than what is described in these guidelines? (Probe: What are the differences? Why do you do it differently?)
7. Have you changed how you manage infant infections in your private practice as a result of this new training? (Probe: If yes, what ‡are the changes? Why or why not?)

Supply chain

8. Describe the availability and supply of drugs for implementing the new guidelines - (Probe: How does this compare to other drugs supplied to UH&FWC?)
9. Have there been any issues with supply? (Probe: any stock outs?) What are the reasons?
10. What changes do you think should be made to the drug supply systems, if any?

Community mobilization

11. What opinions do you have about the community mobilization activities?
12. What concerns came up in community mobilization events? How were these addressed?
13. What successes and challenges have you witnessed in this community mobilization approach? How would you improve the challenges faced?
14. What do you think should be done for community mobilization if they are not aware of community mobilization activities?

Appendix 7. Case follow-up & treatment adherence questionnaire

PROJAHNMO

Implementation Research

This form is to be completed for tracking the child (<60 days) who received treatment/services from union level health facility during last 15 daysfrom thesurveillance period in the site. The name and contact address of the child (cases) will be collected from service register of the union health facility.

1. Address and identification information		
1.01	**Country/Site**	
1.02	**Upazila**	
1.03	**Union**	
1.04	**Village**	
1.05	**Bari**	
1.06	**Household**	
1.11	Child's hospital ID (from service register of H&FWCs)	
1.12	Woman's Current ID	- - -
1.13	Woman's Permanent ID	- - -
1.14	Woman's Name	
1.15	Husband's Name	
1.16	Household Head's Name	
1.17	Contact phone number	

Interviewer's Home Visit					
2.01	Date of visit	|_____|_____|-|_____|_____|-|_____|_____|			
2.02	Day of follow up/tracking	**|_____|th** (between 9th -15th day following the treatment)			
2.03	Interviewer's Name			**Interviewer's code**	|_____|_____|_____||_____|
2.05	Starting time of interview	___ ___:___ ___		Write time in international format	

Section A: Sepsis Case Tracking				
Q#	Question	Coding categories	Code	Skip
A00	Did you visit the UH&FWC (name of the facility) for your	Yes	1	
		No	2	Section B

Section A: Sepsis Case Tracking					
Q#	Question	Coding categories	Code		Skip
	infant in the last 15 days?				
A01	When did you visit the UH&FWC (name of the facility)	Visiting date (dd/mm/yy)	|____|____|-|____|____|-|____|____|		
		Visiting time (24 hour)	__ __ : __ __		
A02	Where were you seen by the provider?	In the FWC exam room	1		
		In the SACMO private chamber	2		
		In the FWV exam room	3		
		In the MO exam room	4		
		Other (specify) _____	5		
		Don't Know	8		
A03	Did you pay money for this visit?	Yes	1		
		No	2		
		Don't Know	8		
A04	What treatment was prescribed by the provider for your infant? <u>Do not prompt at first ;</u> <u>Record all unpromped answers first, then prompt</u>	**Treatment Prescribed**	**Unprompted**	**Prompted**	
		Injection	1	2	
		Antibiotic	1	2	
		Referral	1	2	
		Other (specify) _____	1	2	
		No treatment prescribed	1	2	→A08
		Don't Know	1	2	→A08
A05	If treatment was prescribed by the provider for your infant, what was the name the medicine? <u>Ask the caretaker to show the prescription bottle if available and identifiy from the list.</u> <u>If bottle is not available then indicate caregiver's self-report and circle all that are mentioned.</u>	Gentamicin	1		
		Oral amoxicillin	2		
		Other (specify) _____	3		
		No treatment prescribed	4		→A08
		Don't Know	8		→A07
A06	Data collector: Please indicate if the medicine bottle was available and if any medicine remained in the bottle	Yes, bottle was available and medicine remained in the bottle	1		
		Yes, bottle was available and no medicine remained in the bottle	2		
		No, bottle was not available	3		
		Yes	1		

Section A: Sepsis Case Tracking					
Q#	Question	Coding categories		Code	Skip
A07	Did you pay money for the drug given to your infant by the provider?	No		2	
A08	Did the service provider refer your infant to a higher facility?	Yes		1	
		No		2	→A19
A09	Did the provider give you a referral slip?	Yes		1	
		No		2	
A10	Where did he/she refer your infant?	·(Upazila Health Complex)		1	
		(District Hospital)		2	
		(Medical College Hospital)		3	
		(Other) (Specify)_____ _____		4	
		(Does not know)		5	
A11	Did you agree to go there?	Yes		1	
		No		2	→A14
A12	Did you reach to the referral facility centre according to advice?	Yes		1	
		No		2	→A14
A13	Place and time of arrival at referral facility	Where: _____ __	UHC=1	Other=2	→A15
		Visiting date (dd/mm/yy)	|____|____|-|____|____|-|____|____|		
		Visiting time (24 hour)	__ __ : __ __		
A14	What were the reasons of rejection of referral or you being unable to go to referral facility? <u>Do not prompt</u> <u>Ask what else, multiple answer possible</u>	Didn't think it was necessary to seek care		A	→A19
		Too costly/ Lack of money		B	
		Too far from house		C	
		Transport problem		D	
		No one accompanied		E	
		Not enough time to go		F	
		Family didn't allow me to go		G	
		Service hour inconvenient		H	
		HF found closed/nobody there		I	
		Poor quality of services at facility		J	
		Poor quality & staffs at HF		K	
		Lack of privacy		L	
		Unpleasant behavior at center		M	
		Long queue at HF		N	
		Inadequate drugs at the health center		O	

Section A: Sepsis Case Tracking					
Q#	Question	Coding categories		Code	Skip
		Others: _____ _		X	
A15	What happened after arrival at hospital?	Hospital admission		1	Section B
		How many days? |_____|_____|			
		Referred to higher faciliy		2	→A16
		Admission advised but did not admit the child		3	→A18
		Admission not advised; treatment given		4	Section B
		Did not find doctor at health facility at that time		5	Section B
A16	Did you go to the second referral facility according to advice?	Yes		1	
		No		2	→A18
A17	Place and time of the arrival at the second referral facility.	Where: _____ __	Medical Clg=1	Other=2	Section B
		Visiting date (dd/mm/yy)	|____|____|-|____|____|-|____|____|		
		Visiting time (24 hour)	__ __ : __ __		
A18	Why did not you take the baby at higher facility for better treatment or admit to hospital per advice?	Didn't think it was necessary to seek care		A	Section B
		Too costly/ Lack of money		B	
		Too far from house		C	
		Transport problem		D	
		No one accompanied		E	
		Not enough time to go		F	
		Family didn't allow me to go		G	
		Service hr inconvenient		H	
		HF found closed/nobody there		I	
		Poor quality of services at facility		J	
		Poor quality & staffs at HF		K	
		Lack of privacy		L	
		Unpleasant behavior at center		M	
		Long queue at HF		N	
		Inadequate drugs at the health center		O	
		Others: _____ __		X	
A19	Did the service provider give advice on taking further medication?	Yes		1	
		No		2	
		Don't know/can't remember		8	
		Yes		1	

Section A: Sepsis Case Tracking					
Q#	Question	Coding categories	Code		Skip
A20	Did the service provider ask you to visit the facility to take medication/ drug on the next day?	No	2		→A23
		Don't know/can't remember	8		
A21	Did you visit the UH&FWC on the next day accordingly?	Yes	1		
		No	2		→A23
A22	Was any injection given to your child when you returned to the UH&FWC on that day?	Yes	1		
		No	2		
		Don't know/can't remember	8		
A23	Did the service provider ask you to continute medication at home?	Yes	1		
		No	2		→A27
		Don't know/can't remember	8		→A27
A24	Can you tell me the name of the medicine they asked you to continue administering at home?	Amoxicillin	1		
		Antibiotic	2		
		Other (specify) _____	3		
		Don't know/can't remember	8		
A25	Can you tell me how many days you were instructed to administer the medicine at home?	7 days	1		
		Other (specify) _____	2		
		Don't know/can't remember	8		
A26	Can you tell me how many times a day you were instructed to give the medicine to your infant at home?	Once	1		
		Twice	2		
		Other (specify) _____	3		
		Don't know/can't remember	8		
A27	Did he/she give advice about the signs of illness that required your return to the facility?	Yes	1		→A28
		No	2		→A29
A28	Do you remember any of the danger signs that he/she mentioned?	Yes	1		
		No	2		
A29	What symptoms did your baby have? <u>Do not prompt at first ;</u> <u>Ask what else,</u> <u>Record all unpromped answers first, then prompt</u>	**Danger Sign**	**Unprompted**	**Prompted**	
		Severe chest in-drawing	1	2	
		Lower temperature/ Hypothermia	1	2	
		Fever or Raised temperature	1	2	
		Poor or no sucking reflex	1	2	
		Unconscious or drowsy	1	2	

Section A: Sepsis Case Tracking					
Q#	Question	Coding categories	Code		Skip
		Less movement than normal/ movement only when stimulate	1	2	
		Central cyanosis	1	2	
		Convulsion /history of convulsions	1	2	
		Persistent vomiting/unable to feed	1	2	
		Bulging fontanelle	1	2	
		Others 1.	1	2	
		Others 2.	1	2	
A30	Did the service provider tell you they would provide follow-up phone calls or home visits?	Yes	1		
		No	2		
		Don't know/can't remember	8		
A31	Did anyone from UH&FWC call you/your husband/family to ask about your infant after the initial visit?	Yes	1		
		No	2		
		Don't know/can't remember	8		
A32	What did he/she talk/ask about?	Current status of the child	1		
		Importance of completing the full course of antibiotic/medication	2		
		Danger sign/when to return to hospital	3		
		Other (specify) _____	4		
		Don't know/can't remember	8		
A33	Did the provider advise you to take the baby back to the facility during this follow-up contact?	Yes	1		
		No	2		
		Don't know	8		
A34	Did anyone visit your household and ask about current condition of the yor child after the initial visit?	Yes	1		
		No	2		Section B
		Don't know/can't remember	8		
A35	Please tell me the particulars of the visiting service provider.	Who? Name: _____	Don't know=8		
		Designation: _____	Don't know=8		
		Visiting day (dd/mm/yy)	|____|____|-|____|____|-|____|____|		
		Visiting time (24 hour)	__ __ : __ __		
A36	What did he/she talk/ask about?	Current status of the child	1		
		Importance of completing the full course of antibiotic/medication	2		

Section A: Sepsis Case Tracking				
Q#	Question	Coding categories	Code	Skip
		Danger sign/when to return to hospital	3	
		Other (specify) _____	4	
		Don't know/can't remember	8	
A37	Did he/she physically examine your child?	Yes	1	
		No	2	
		Don't know/can't remember	8	
A38	Did the provider advise you to take the baby back to the facility during this follow-up visit?	Yes	1	
		No	2	
		Don't know/can't remember	8	
A39	Did the provider prescribe any different medicine during these follow-up visits?	Yes	1	
		No	2	
		Don't know	8	

Section B: Caregiver Adherence and Self-Efficacy				
Q#	Question	Coding Category	Code	Skip
B01	For this episode of your infant's illness, did you or another family member administer medicine to the infant at home?	Yes	1	
		No	2	→B14
		Don't know/can't remember	8	→B14
B02	Were you the person primarily responsible for giving medicine to the infant?	Yes	1	→B04
		No	2	→B03
		Don't know/can't remember	8	→B03
B03	If the respondent was not the person primarily responsible for giving medicine to the infant, who was?	Infant's mother	1	
		Infant's father	2	
		Infant's grandmother/grand father	3	
		Sister /brother	4	
		Other (specify) _____	5	
		Don't know/can't remember	8	
B04	Did you ever forget to administer medication to your baby?	Yes	1	
		No	2	
		Don't know/can't remember	8	
	How often did you have difficulty remembering	Very often	1	
		Sometimes	2	

B05	to give the baby his/her medicine? Prompt each response first as options and the record	Did not have trouble remembering	3	
		Don't know/can't remember	8	
B06	Sometimes parents do not administer medication as directed for reasons other than forgetting. Were there any days that you did not administer medication for other reasons?	Yes	1	
		No	2	
		Don't know/can't remember	8	
B07	Did you ever feel it was an inconvenience to adhere to the medication schedule?	Yes	1	
		No	2	
		Don't know/can't remember	8	
B08	Did you ever stop administering medication to your baby because they had a negative side effect when they took the medication?	Yes	1	
		No	2	
		Don't know/can't remember	8	
B09	Did you ever stop administering medication to your baby because they seemed to not be sick anymore?	Yes	1	
		No	2	
		Don't know/can't remember	8	
B10	When administering the medication, how confident were you in your ability to properly give the medication to the infant?	Very confident	1	
		Somewhat confident	2	
		Not confident	3	
		Don't know/can't remember	8	
B11	How confident were you in your ability to administer the medication every day as instructed by the provider?	Very confident	1	
		Somewhat confident	2	
		Not confident	3	
		Don't know/can't remember	8	
B12	How confident were you in your ability to administer the medication more than one time each day as instructed by the provider?	Very confident	1	
		Somewhat confident	2	
		Not confident	3	
		Don't know/can't remember	8	
B13	How confident were you in your understanding of the	Very confident	1	
		Somewhat confident	2	

	provider's instructions for administering the medication at home?	Not confident	3		
		Don't know/can't remember	8		
B14	How confident were you in your ability to identify the following signs of illness in your infant? <u>Prompt for each symptom and circle the corresponding number for each response</u>	**Danger Sign**	**Very Confident**	**Some what Confident**	**Not Confident**
		Severe chest in-drawing	1	2	3
		Lower temperature/ Hypothermia	1	2	3
		Fever or Raised temperature	1	2	3
		Poor or no sucking reflex	1	2	3
		Unconscious or drowsy	1	2	3
		Less movement than normal/ movement only when stimulate	1	2	3
		Central cyanosis	1	2	3
		Convulsion /history of convulsions	1	2	3
		Persistent vomiting/unable to feed	1	2	3
		Bulging fontanelle	1	2	3
		Skin pustules	1	2	3
		Pus/foul smelling discharge from umbilicus/ Red and swollen	1	2	3
B15	What is the current status of your child?	Alive and recovered at home	1	→C01	
		Sick and at home	2	→C01	
		Sick and admitted at hospital	3	→B16	
		Not alive	4	→B17	
B16	If B1(2), date and time of hospital admission	Visiting day (dd/mm/yy)	|____|____|- |____|____|- |____|____|		
		Visiting time (24 hour)	__ __ : __ __		
B17	If B15(4), date, time and causes of death	Date (dd/mm/yy)	|____|____|- |____|____|- |____|____|		

		Time (24 hour)	__ __ : __ __
		Causes: * * *	
C01	Ending time of interview	___ ___:___ ___	
C02	Visit Outcome	Interview Completed……. 01 Interview incomplete……. 02 Respondant absent……. 03 Refused to give interview …04 Migrated out…… 05 Household destroyed…… 06 Others (specify)_____ 77	If the outcome code between 03-06 then plan for one return visit and indicate below (C03)
C03	Date of Next Visit	|_____|_____|- |_____|_____|- |_____|_____|	

End the interview with thanks. Before leaving the interview place, carefully check whether all the answers of the questions have been properly recorded.

_____

_____

Signature of data collector

Date:____/____/_____

____/____/_____

Signature of reviewer

Date:

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Zanichelli, Veronica, et al. "Patient-Related Determinants of Antibiotic Use: A Systematic Review." *Clinical Microbiology and Infection* 25 1 (2019): 48-53.

Curriculum Vitae

Jennifer A. Applegate

PERSONAL DATA

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USA
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EDUCATION AND TRAINING

Ph.D. Candidate, expected January 2020	Johns Hopkins Bloomberg School of Public Health. Department of International Health, Global Disease Epidemiology and Control. Baltimore, Maryland, USA Dissertation: Early implementation of guidelines for managing young infants with infection in rural Bangladesh: A mixed methods implementation research study
M.S.P.H., 2012	Johns Hopkins Bloomberg School of Public Health. Department of International Health, Global Disease Epidemiology and Control. Baltimore, Maryland, USA • Vaccine Science and Policy Certificate Program
B.S., 2007	The University of Georgia. Psychology. Athens, GA
B.S., 2007	The University of Georgia. Child and Family Development. Athens, GA

PROFESSIONAL EXPERIENCE

Johns Hopkins Bloomberg School of Public Health
Department of International Health, International Center for Maternal and Newborn Health
Baltimore, MD, USA
Doctoral Fellow, September 2014-Currently

Principal responsibilities: Doctoral student investigator on *Implementation research to support Bangladesh Ministry of Health and Family Welfare (MOHFW) to implement its national guidelines of management of infections in young infants in two rural districts of Bangladesh*; Collaborated with PI and in-country partners to identify implementation research questions and outcomes, plan implementation strategies, and design embedded mixed methods evaluation; Served as IRB point person for research protocol, consent forms, and reporting to JHSPH IRB; Led development of survey tools, semi-structured interview guides and data collection manuals for embedded mixed methods evaluation; Supported fieldwork and primary data collection in primary health facilities and conducted key-informant interviews with high-level managers in MOHFW; Led analysis of quantitative and qualitative data for periodic stakeholder meetings, writing of technical reports and development of presentations working with in-country partners

Johns Hopkins Bloomberg School of Public Health
Department of International Health, Strategic Policy Program of ReAct-Action on Antibiotic
Baltimore, MD, USA

Research & Policy Fellow, August 2018-Currently

Principal responsibilities: Support research on antimicrobial resistance (AMR) in both healthcare and agricultural sectors; Literature review of the role of gender in AMR; Collaborated with Dr. Anthony So as a member of the teaching team for a doctoral-level course on tackling the intersectoral challenge of AMR from a systems thinking perspective and utilizing a policy analytical framework for student assignments

USAID's MaMoni Health System Strengthening (HSS) Project-Bangladesh
Baltimore, MD with travel to Dhaka, Bangladesh
Consultant, October 2017-September 2018

Principal responsibilities: Conducted analysis of program data for MaMoni HSS' support to Bangladesh MOHFW to implement the national guidelines for managing infections in young infants at primary health facilities; Collaborated with MaMoni HSS team to conduct interviews with health workers and government managers, develop a final technical report and brief sharing findings and recommendations; Led the development and submission of a manuscript including analysis of service delivery data, interviews with government providers and managers, and program documentation

Johns Hopkins Bloomberg School of Public Health
Department of International Health, International Center for Maternal and Newborn Health
Baltimore, MD, USA with travel to Bangladesh and Tanzania
Senior Research Program Coordinator II, September 2012-August 2015

Principal responsibilities: Collaborated with study teams to obtain approvals from IRB including development of research protocols, consent forms, amendments and annual progress reports; Supported development of grant proposals for USAID, NIH, Bill & Melinda Gates Foundation; Worked with financial teams to develop SOW & deliverable schedules for sub-contracts and monitor project budgets; Coordinated with local partners to arrange stakeholder meetings to disseminate study findings; Supported development of technical reports, conference presentations, and annual workplans for USAID-funded studies

USAID's Maternal & Child Health Integrated Program (MCHIP)
Jhpiego, Postpartum Family Planning Program
Baltimore, MD
Internship in Jharkhand, India, June-August 2011

Principal responsibilities: Supported a process evaluation of MCHIP's Standards-Based Management and Recognition (SBM-R) quality improvement strategy for postpartum family planning programs in three target districts of Jharkhand, India; Prepared a technical report and brief of recommendations to address gaps in service delivery based on interviews with district hospital providers and Jhpiego program officers

Johns Hopkins Bloomberg School of Public Health
Department of International Health, Global Disease Epidemiology and Control Program
Baltimore, MD, USA
Research Assistant, September 2010-September 2012

Principal Responsibilities: Conducted systematic literature reviews, data abstraction and meta-analyses for articles on global diarrhea morbidity and mortality in children; Analyzed DHS & MICS survey data for changes in diarrhea indicators & treatment to inform manuscript development

University of Georgia

Department of Entomology
Athens, GA
Research Assistant, 2009-2010

Principal responsibilities: Conducted narrative interviews with individuals suffering from Delusory Parasitosis/ Ekbom Syndrome (DP/ES); Coded and maintained a database of qualtiative data

Cornerstone's Counseling
Cleveland, GA
Parent Aide, 2008-2010

Principal responsibilities: Informed clients with open cases with the Department of Family and Children's Services and/or Department of Juvenile Justice about maternal and pediatric health issues including child nutrition, pre- and postnatal care, and parenting skills; Served as liaison between clients and caseworkers; Provided family planning counseling and connected women with reproductive health services

PROFESSIONAL ACTIVITIES

EDITORIAL ACTIVITIES

BMC Pediatrics (2018-2019): Reviewed 5 manuscripts focusing on MNCH in low-resource settings

HONORS AND AWARDS

Honors

- MSPH Student Member of the International Health Curriculum and Credentials Committee (2011-2012)
- Phi Kappa Phi Fellowship Nominee for the University of Georgia (2010)

Awards

- Travel award recipient for Partnerships, Policy and Progress Conference at McGill University (2016)
- Global Health Established Field Placement Award (2011)

PUBLICATIONS

1. Walker, CL., **Applegate, JA**., & Black, RE. (2012). *Haemolytic-uraemic syndrome as a sequela of diarrhoeal disease.* J Health Popul Nutr, 30(3), 257-261.

2. Baqui AH, Rosen HE, Lee AC, **Applegate JA**, El Arifeen S, Rahman SM, Begum N, Shah R, Darmstadt GL, Black RE. *Preterm birth and neonatal mortality in a rural Bangladeshi cohort: implications for health programs.* J Perinatol. 2013 Dec;33(12):977-81. doi: 10.1038/jp.2013.91. Epub 2013 Aug 15. PubMed PMID: 23949837.

3. **Applegate JA,** Fischer Walker CL, Ambikapathi R, Black RE. *Systematic review of probiotics for the treatment of community-acquired acute diarrhea in children.* BMC Public Health. 2013;13 Suppl 3:S16. doi: 10.1186/1471-2458-13-S3-S16. Epub 2013 Sep 17. Review. PubMed PMID: 24564646; PubMed Central PMCID: PMC3847198.

4. Shah R, Mullany LC, Darmstadt GL, Mannan I, Rahman SM, Talukder RR, **Applegate JA**,

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11. **Applegate JA**, Ahmed SA, Harrison M, Callaghan-Koru JA, Mousumi M, Begum N, Moin M, Joarder T, Ahmed S, George J, Mitra DK, Ahmed N, Shahidullah M, Baqui AH. *Caregiver acceptability of the guidelines for managing young infants with possible serious bacterial infections (PSBI) in primary care facilities in rural Bangladesh: a mixed methods implementation research study.* Submitted to PLoS one (Under review, November 2019)

PRACTICE ACTIVITIES

Traveled to Jakarta, Indonesia (May 2015) to support Universitas Indonesia in developing a proposal for USAID's Partnerships for Enhanced Engagement in Research (PEER): *Development of a Referral System using Kangaroo Mother Care (KMC) Intervention for Low Birth Weight Babies in Jakarta and West Java, Indonesia* (Awarded-August 2015)

Presented early findings from doctoral thesis project to global stakeholders in the following meetings:

- WHO-sponsored "Meeting of Principal Investigators for PSBI Implementation Research" in Lagos, Nigeria (November 30-December 4, 2016). Presented early findings from our implementation research study site in Bangladesh to inform operationalization of WHO guidelines, *Managing possible serious bacterial infection in young infants when referral is not feasible.*

- Canadian Network for Maternal, Newborn and Child Health's "Partnerships, Policy and Progress Conference" at McGill University, Montreal, Canada (November 3-4, 2016). Poster Presentation.

- Meeting to Review Early Lessons and Observations from Newborn and Young Infant's Sepsis Management Studies in Bangladesh. Dhaka, Bangladesh (January 25, 2016). Presented early findings to Bangladesh MOHFW and implementing partners to identify barriers and facilitators to implementation and develop recommendations for adjusting implementation strategies for national guidelines, *Management of Infection of the 0-59 Days Infants at Union Level Facilities and NGO Clinics without Indoor Facilities*

TEACHING

Teaching Assistant, course: Tackling the Intersectoral Challenge of Antimicrobial Resistance: Problem Solving Seminar
Department of International Health, Johns Hopkins Bloomberg School of Public Health, 3rd term, 2019

Teaching Assistant, course: Health Information Systems
Department of International Health, Johns Hopkins Bloomberg School of Public Health, 2nd term, 2018, 2019

Teaching Assistant, course: Global Health Principles and Practices
Johns Hopkins University, 2nd Semester, 2017

Teaching Assistant, course: Issues in the Reduction of Maternal and Neonatal Mortality in Low Income Countries
Department of International Health, Johns Hopkins Bloomberg School of Public Health, 2nd term, 2016

Teaching Assistant, course: Large-Scale Effectiveness Evaluations of Health Programs
Department of International Health, Johns Hopkins Bloomberg School of Public Health, 4th term, 2015

Teaching Assistant, course: Global Disease Control Programs and Policies
Department of International Health, Johns Hopkins Bloomberg School of Public Health, 4th term, 2011, 2012, 2014

Teaching Assistant, course: Introduction to International Health
Department of International Health, Johns Hopkins Bloomberg School of Public Health, 1st term, 2011, 2012